(2011) estimated the effect size to be -0.6 (SE 0.2) for a 1 μg/dL increase in concurrent PbB (mean 8.1 μg/dL ±4.4 SE). Prospective studies conducted in Cleveland, Ohio (Min et al. 2009) and Rochester, New York (Jusko et al. 2008) also found similar effect sizes for the associations between increasing PbB and decreasing IQ. In the Rochester study, the changes in FSIQ were larger at lower PbB, consistent with the outcomes of the Lanphear et al. (2005) study (Jusko et al. 2008). For the PbB range 2.1–10 μg/dL, the change in FSIQ measured at age 6 years was -1.2 per 1 μg/dL increase in PbB. This decreased to -0.32 and -0.15 for the ranges 10–20 and 20–30 μg/dL, respectively. In the Cleveland study, the change was -0.50±0.20 (SE) in FSIQ measured at age 4 years per 1 μg/dL increase in concurrent PbB (Min et al. 2009). A study conducted in Detroit, Michigan estimated the change in FSIQ to be -0.20 per 1 SD change in PbB (Chiodo et al. 2004). The decrement was significant ($p \leq 0.05$) in PbB strata <7.5 and <10 μg/dL.

A cross-sectional study conducted in South Korea evaluated PbB and FSIQ in 1,001 children 8–11 years of age (Hong et al. 2015). The estimated effect of PbB on FSIQ was -7.23 points (95% CL -13.39, -1.07) per 10-fold increase in PbB. The 5^{th}–95^{th} percentile range for the cohort PbB was 0.53–6.16 μg/dL.

Cognitive function in early childhood–other than FSIQ. Several studies have examined outcomes other than IQ and have found associations between PbB and changes in cognitive function in children whose PbBs were <10 μg/dL (Table 2-30). These include prospective studies that used the same outcome metric, the BSID MDI, allowing comparison of outcomes across studies (Dietrich et al. 1986, 1987, 1989; Kim et al. 2013b, Tellez-Rojo et al. 2006). A prospective study of 884 children conducted in South Korea found negative associations between PbB in late pregnancy (geometric mean 1.3±1.5, geometric standard deviation [GSD]) and MDI scores measured at age 6 months (Kim et al. 2103b). A prospective study of 294 children conducted in Mexico City found negative associations between concurrent PbB (mean 4.27±2.14, SD) and MDI measured at 24 months in a PbB stratum <10 μg/dL (Tellez-Rojo et al. 2006). A prospective study conducted in Cincinnati, Ohio (approximately 190 infants) also found declines in MDI scores at age 6 and 12 months in association with increasing maternal, neonatal, or infant PbB (Dietrich et al. 1986, 1987, 1989).

Several large-scale retrospective studies linked academic performance for individual children with their corresponding blood Pb data recorded in state or local blood Pb registries (Evens et al. 2015; Miranda et al. 2009; Zhang et al. 2013; Table 2-30). Evens et al. (2015) linked individual 3^{rd} grade Illinois Standard Achievement Test (ISAT) scores and PbB data (birth–72 months) for a population of 47,158 children in Chicago, Illinois. All children had PbB <10 μg/dL and the population mean was 4.8±2.2 μg/dL (SD).

Increasing PbB was negatively associated with decreasing covariate adjusted scores in math and reading. The adjusted relative risks (RRs) for failing scores was also significant for a 1 or 5 μg/dL increase in PbB. Miranda et al. (2009) linked 4th grade reading End of Grade (EOG) scores and PbB data collected (birth–36 months) for a population of 57,678 children in North Carolina. The population mean PbB was 4.8 μg/dL (range 1–16 μg/dL); 94% of children had PbB <10 μg/dL. Increasing PbB was associated with decreasing covariate adjusted scores in all PbB strata, the lowest of which was 2 μg/dL. The effect size (change in score/μg/dL PbB) increased with increasing PbB. Zhang et al. (2013) linked Michigan Educational Assessment Program (MEAP) scores and PbB data (birth–72 months) of age for a population of approximately 21,000 children in Detroit, Michigan. Covariate adjusted ORs for failing scores in mathematics, science, and reading were significant for PbB strata 1–5, 6–10, and >10 μg/dL. A cross-sectional study of data from NHANES III examined associations between PbB and scores on tests of cognitive function (Wide Range Achievement Test-Revised [WRAT-R], Wechsler Intelligence Scales for Children-Revised [WISC-R]) in approximately 5,000 children 6–16 years of age (Lanphear et al. 2000a). Increasing PbB was significantly associated with decreasing scores in reading in blood strata <5.0, <7.5, and <10 μg/dL. McLaine et al. (2013) examined associations between PbB (9–72 months) and kindergarten readiness assessed from Phonological Awareness Literacy Screening-Kindergarten (PALS-K) scores in approximately 3,400 children in Providence, Rhode Island. The population median PbB was 4.2 μg/dL (interquartile range 2.9–6.0); 93% of children had PbB <10 μg/dL. Mean difference in covariate adjusted scores in blood strata 5–9 and ≥10 μg/dL compared to <4 μg/dL were in the negative direction and adjusted prevalence ratios for test failure was significant in both strata.

Altered mood and behavior. Numerous studies have examined possible associations between neonatal and child PbB risk of behaviors that may contribute to learning deficits, including attention deficits, hyperactivity, autistic behaviors, conduct disorders, and delinquency (Table 2-30).

Several studies have examined attention-deficit/hyperactivity disorder (ADHD) as an outcome, allowing comparisons of outcomes across studies (Boucher et al. 2012; Braun et al. 2006; Choi et al. 2016; Froehlich et al. 2009; Hong et al. 2015; Wang et al. 2008). Collectively, the ADHD studies indicate that risk of childhood ADHD increases in association with increasing PbB <10 μg/dL (Table 2-30). In a case-control study conducted in China (630 cases), covariate adjusted ORs for ADHD in children 4–14 years of age were 4.92 (95% CL 3.47, 6.98) for the PbB range 5–10 μg/dL and 6.00 (4.11, 8.77) for PbB ≥10 μg/dL compared to <5 μg/dL (Wang et al. 2008). A prospective study of 272 children (mean age 11 years) conducted in Nunavik, Canada found elevated covariate adjusted ORs of 4.01 (95% CL 1.06, 15.23) for a PbB stratum 1.6–2.7 μg/dL and 5.52 (95% CL 1.38, 22.12) for the stratum 2.7–12.8 μg/dL

(Boucher et al. 2012). A longitudinal study examined ADHD outcomes of 2,159 South Korean children (ages 7–9 years) who did not exhibit ADHD symptoms at recruitment (Choi et al. 2016). Two years following baseline assessment, the covariate adjusted relative risk of ADHD was estimated to be 1.552 (95% CL 1.002, 2.403) for children having PbB ≥2.17 μg/dL compared to ≤2.17 μg/dL. The geometric mean PbB for the cohort was 1.62 μg/dL ±1.52 (GSD). Several cross-sectional studies have also found associations between concurrent PbB and risk of ADHD (Braun et al. 2006; Froehlich et al. 2009; Hong et al. 2014). A study of data on approximately 4,700 children (age 4–15 years) reported in the 1999–2002 NHANES found elevated risk of ADHD in association with concurrent PbB >2 μg/dL and a significant trend in risk with increasing PbB (Braun et al. 2006). Froehlich et al. (2009) examined data for children 8–15 years of age from the 2001–2004 NHANES. Covariate adjusted ORs of ADHD were elevated for the PbB stratum >1.3 μg/dL (compared to ≥0.8 μg/dL). A cross-sectional study conducted in South Korea examined associations between PbB and ADHD rating scores of 1,001 children of age 8–11 years (Hong et al. 2015). One $\log_{10}$ increase of PbB was associated with increases in teacher-rated ADHD hyperactivity (OR 3.66; 95% CI 1.18, 6.13) and total ADHD score (OR 6.38; 95% CI 1.36, 11.40). The cohort geometric mean PbB was 1.8±1.4 μg/dL (SD).

Prospective studies have also provided evidence for associations between neonatal or early childhood PbB and other neurobehavioral outcomes, including neonatal behavior, sleep disorders, hyperactivity, autistic behavior, and delinquency (Dietrich et al. 2001; Kim et al. 2016; Liu et al. 2014b, 2015b; Sioen et al. 2013).

Altered neuromotor-neurosensory function. Numerous studies have examined possible associations between neonatal and child PbB and neuromotor or neurosensory function (Table 2-30). Several studies used the Psychomotor Development Index (PDI) score from the BSID, allowing comparison of results across studies (Dietrich et al. 1987, 1989; Kim et al. 2013b; Tellez-Rojo et al. 2006). Each study found negative associations for PDI scores measured from 6 to 12 months in association with increasing prenatal (e.g., maternal) or neonatal PbB. Studies that repeatedly measured PDI scores longitudinally within the same birth cohorts found that associations observed at 6 months persisted to later ages (Dietrich et al. 1987, 1989, 1991; Tellez-Rojo et al. 2006). A prospective study conducted in China administered a neurobehavioral test battery to a birth cohort of 237 children at age 7 years (Chiodo at al. 2004). Significant declines in performance ($p \leq 0.05$) were observed in PbB strata that ranged from <3 μg/dL at the lowest to <10 μg/dL; most tests that showed significant declines at <10 μg/dL, also showed declines at <5 μg/dL ($p \leq 0.05$). A prospective study conducted in Nunavik, Canada evaluated fine motor control in a birth cohort at 5 years (Fraser et al. 2006). Significant changes in motor control

assessed from sway and reaction times were associated with increasing concurrent PbB ($p \leq 0.01$). The cohort PbB mean was 5.3 μg/dL ±4.9 (SD). This birth cohort also exhibited changes in visual evoked potentials that were associated in increasing cord PbB (Ethier et al. 2012). The cohort cord PbB mean was 4.6±3.1 (SD).

Altered brain structure and neurochemistry. A follow-up to the Cincinnati prospective study (Dietrich et al. 1986) estimated whole brain volumes and imaged brain metabolites in 157–159 adults at age 19–24 years (Brubaker et al. 2010; Cecil et al. 2008, 2011; Table 2-30). Decreasing covariate adjusted brain volume was associated with increased childhood mean PbB (measured between ages 6 months and 6 years). Brain volume reductions that were associated with childhood PbB compromised approximately 1.2% of the total gray matter and were more severe in males compared to females. The largest effects were observed in the anterior cingulate cortex. This region of the brain is involved in controlling executive function, mood, and decision-making. Increasing childhood PbB was also associated with decreasing concentrations of various metabolites in brain known to be important in supporting metabolic structural integrity of neurons (e.g., lipid metabolism and myelin production). These included decreased N-acetyl aspartate (NAA) in the basal ganglia and cerebellar hemisphere, decreased glutamate-glutamine in the vermis and parietal white matter, decreased creatine and phosphocreatine in the basal ganglia, and decreased cholines in the cerebellum, parietal white matter, and frontal white matter. These changes in association with childhood PbB suggest that childhood Pb exposure may be indicators of longer-term changes in brain glutamate-associated lipid metabolism or neuronal architecture (Cecil et al. 2011).

Associations Between Bone Pb and Neurological Effects in Children. Few studies have been conducted to assess possible associations between bone Pb and neurological function in children (Table 2-31). Prospective studies of outcomes in children of mother-infant pairs have found associations between maternal or child bone Pb cognitive function (Campbell et al. 2000b; Gomaa et al. 2002; Needleman et al. 1996; Wasserman et al. 2003; Xu et al. 2015). Increasing bone Pb measured at age 24 months was associated with decrements in cognitive development (Gomaa et al. 2002) and behaviors indicative of attention deficit hyperactivity disorder assessed at age 7–15 years (Xu et al. 2015). Increasing child bone Pb measured later in childhood (ages 11–14 years) was associated with decrements in language processing (Campbell et al. 2000b); full scale, verbal, and performance IQ (Wasserman et al. 2003); and delinquent, aggressive, internalizing, externalizing behaviors (Needleman et al. 1996). A case-control study of adjudicated delinquency at age 12–18 years found associations between increasing bone Pb and delinquency (Needleman et al. 2002).

Table 2-31. Associations Between Bone Pb and Neurological Outcomes in Children

		Neurological outcome			
Reference	Population	Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Campbell et al. 2000b	156 males, age: 11–14 years	↑ T	–	–	Language processing
Gomaa et al. 2002	197 mother-infant pairs	↑ P[a] 0 T[a]	–	–	24-month MDI[b]
Needleman et al. 1996	301 males, age: 9–13 years	–	–	↑ T	Delinquent, aggressive, internalizing, externalizing behaviors
Needleman et al. 2002	194 male cases, 145 controls, age: 12–18 years	–	–	↑ T	Adjudicated delinquency
Wasserman et al. 2003	167 children, age: 10–12 years	↑ T	–	–	IQ (full scale, verbal, performance)[c]
Xu et al. 2015	197 mother-infant pairs	–	–	↑ P[a]	Attenuation of effect of maternal self-esteem on ADHD assessed at age 7–15 years[d]

[a]Maternal bone lead measured within 1 month of birth.
[b]Bayley Scale.
[c]Wechsler Intelligence Scale for Children-III.
[d]Maternal self-esteem was evaluated with Coopersmith Self-Esteem Inventory. ADHD was evaluated with Conners' Parent Rating Scale-Revised and Behavior Rating Inventory of Executive Function.

↑ = positive association; ↓ = negative association; 0 = no association; – = not reported; ADHD = Attention deficit hyperactivity disorder; C = calcaneous bone; MDI = Mental Developmental Index; P = patella; Pb = lead; T = tibia; O = other

Effects at Blood Pb Levels ≤10 µg/dL in Adults. Numerous longitudinal and large cross-sectional studies in adults provide a weight of evidence for decreased cognitive function, altered mood and behavior, and altered neuromotor and neurosensory function in association with exposures that result in PbB <10 µg/dL, with some studies showing effects in the 3–5 µg/dL range. Study details are reviewed in the *Supporting Document for Epidemiological Studies for Lead,* Table 10. Cognitive, neuromotor, and neurosensory outcomes have been evaluated with tests of memory, learning, executive function, reaction time, walking

speed, and tremor. Pb exposure has been associated with risk of various psychiatric symptoms including anxiety, depression, and schizophrenia, and with risk of ALS. In some studies, associations were found between outcomes and PbB and/or bone Pb. Several studies have examined cohorts of people who had mean ages within the range 50–70 years. Studies of cognitive function in elderly populations must control for factors that contribute to age-related decrements in function, including confounding from the relationship between age and bone Pb, which increases with age. Longitudinal studies offer advantages over cross-sectional studies in that they can provide measurement changes in function of individual subjects with age.

Cognitive function. Numerous studies have examined possible associations between Pb exposure and cognitive function in adults (Table 2-32). Most of these studies have found associations between increasing Pb exposure, indicated by blood or bone Pb, and indications of decreased cognitive function (Muldoon et al. 1996; Payton et al. 1998; Power et al. 2014; Seegal et al. 2013; Seo et al. 2014; Shih et al. 2006; Weisskopf et al. 2007; Weuve et al. 2006, 2009; Wright et al. 2003b). However, one of the largest cross-sectional studies analyzed data from NHANES III (1988–1994) and found no associations between PbB and performance neurobehavioral tests (Krieg et al. 2005). This study compared scores from several tests from the Neurobehavioral Evaluation System (NBES) and concurrent PbB in approximately 5,700 adults (age 20–50 years). Implemented tests measured processing speed, attention, learning, and memory (reaction time, symbol-digit substitution, serial digit learning). The geometric mean PbB was 2.51 μg/dL (range 0.7–42) and 96% of the cohort was <10 μg/dL. No significant associations (defined as $p \leq 0.05$) between PbB and cognitive outcomes were found. Several studies have examined smaller cohorts from longitudinal studies designed to evaluate health in aging populations. Studies of male cohorts of from the Normative Aging Study have found significant ($p \leq 0.05$) associations between increasing blood and/or bone Pb and decreasing scores on cognitive tests, including short-term memory, verbal memory, and visuoconstruction (Payton et al. 1998; Weisskopf et al. 2007; Weuve et al. 2006). Cohort sizes in these studies ranged from approximately 600 to 1,100 and the mean PbB ranged from 2.9±1.9 to 5.5±3.5 μg/dL. Weuve et al. (2006) found that decreases in cognitive performance were associated with PbB in a cohort of ALAD-2 carriers, but not in a cohort that carried the wildtype ALAD allele. Studies of female cohorts (approximately 600 subjects) from the longitudinal Nurses' Health Study have found mixed outcomes (Power et al. 2014; Weuve et al. 2009). Weuve et al. (2009) found significant association between increasing tibia Pb, but not PbB, and scores on a telephone survey of cognitive function (the Telephone Interview for Cognitive Status, TIC). The TIC has been used to assess memory and executive function and has been used to evaluate dementia. The effect size was -0.051 (95% CL -0.099, -0.003) points per 1 SD of tibia Pb. Power et al. (2014) used the same telephone survey

instrument and found no associations between blood or bone Pb and cognitive function; the effect size for PbB was -0.013 (95% CL -0.044, 0.017) and the cohort mean PbB was 2.9±1.9 (SD) μg/dL. A cross-sectional study of approximately 1,000 adults from the Boston Memory Study found negative associations ($p \leq 0.05$) between performance on cognitive tests and increasing tibia Pb, but not for PbB (Shih et al. 2006). The cohort mean blood Pb was 3.46±2.2 (SD) μg/dL. Cognitive function evaluated included language, processing speed, executive function, verbal memory and learning, and visuoconstruction. The effect sizes were substantially attenuated by race/ethnicity and years of educational and were no longer significant ($p<0.05$) when adjusted for these covariates. A cross-sectional study of approximately 500 adult females from the Study of Osteoporotic Fractures found significant associations ($p \leq 0.05$) between performance on cognitive tests and increasing PbB (Muldoon et al. 1996). The odds of performing worse on visual attention and short-term memory tests were significantly decreased ($p \leq 0.05$) in a PbB stratum 4–7 and to >7 μg/dL compared to stratum <4 μg/dL.

Altered mood and behavior. Several studies have examined associations between Pb exposure assessed from blood or bone Pb and symptoms of psychiatric disorders (Table 2-32). Several studies have analyzed cross-sectional data from NHANES to explore associations between depression symptoms and PbB (Bouchard et al. 2009; Buser and Scinicariello 2017; Golub et al. 2010; Scinicariello and Buser 2015). Three studies found associations between PbB and depression in adult populations that had geometric mean PbBs that were 2–3 μg/dL compared to populations that have PbBs <1 (Bouchard et al. 2009; Buser and Scinicariello 2017; Golub et al. 2010). Buser and Scinicariello (2017) found stronger associations in adult women than in men. Associations between psychiatric disorders and Pb exposure metrics have also been studied in longitudinal studies (Rajan et al. 2007; Rhodes et al. 2003). Two studies of cohorts from the Normative Aging Study found significant ORs for blood or bone Pb and various psychiatric symptoms in males (mean age 67±7, SD), including somatization, phobic anxiety, and composite indices of distress. Mean PbBs in these cohorts were 6±4 (SD) μg/dL. Associations between PbB and psychiatric disorders have also been found in case-control studies (Opler et al. 2004, 2008). The largest was a study of 71 schizophrenia cases and 129 matched controls (Opler et al. 2008). The adjusted OR for schizophrenia was 1.92 (95% CI 1.05, 3.87) for the PbB stratum ≥15 μg/dL compared to 15 μg/dL. Because individual PbB data were not available, subjects were categorized into the high (<15 μg/dL) or low (15 μg/dL) PbB categories based on measurements of serum ALA and a regression model relating PbB and ALA derived from a different population (Graziano et al. 1990). Although the accuracy of the method for assigning subjects from Graziano et al. (1990) into low or high categories was, on average, approximately 90%, uncertainty in the actual regression model is likely to have resulted in some misclassification of individuals.

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Cognitive abilities			
Krieg et al. 2005 Cross-sectional study, n=5,662 adults, age 20–59 years	Gmean (range): 2.51 (0.7, 41.8)	Simple visual reaction time	No associations between PbB and performance scores • Mean reaction time: p=0.24
		Symbol-digit substitution	• Mean total latency: p=0.27 • Number of errors: p=0.82
		Serial digit learning	• Trials to criterion: p=0.26 • Total score: p=0.24
Muldoon et al. 1996 Cross-sectional study, n=530 adult women, mean age 70 years	Mean (SD): • All: 4.8 (0.4) • Rural: 4.5 (0.4) • Urban: 5.4 (0.4) • Low: 4 • Medium: 4–7 • High: >7	Trailmaking B	• **Urban** ○ Medium PbB OR: 0.97 (0.40, 2.40) ○ High PbB OR: 0.79 (0.20, 3.04) • **Rural** ○ **Medium PbB OR: 2.05 (1.05, 4.02)*** ○ **High PbB OR: 2.60 (1.04, 6.49)***
		Digit symbol (correct)	• **Urban** ○ Medium PbB OR: 0.61 (0.25, 1.50) ○ High PbB OR: 0.64 (0.16, 2.47) • **Rural** ○ **Medium PbB OR: 2.03 (1.06, 3.88)*** ○ **High PbB OR: 3.73 (1.57, 8.84)***
		Incidental memory	• **Urban** ○ Medium PbB OR: 0.50 (0.22, 1.16) ○ High PbB OR:0.99 (0.28, 1.16) • **Rural** ○ Medium PbB: OR: 1.37 (0.77, 2.41) ○ High PbB: OR: 1.89 (0.83, 3.41)

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Payton et al. 1998 Longitudinal study, n=141 males, mean age 67 years	Mean (SD): • 5.5 (3.5) • Q1: 1.4 • Q2: 3.5 • Q3: 5.4 • Q4: 9.8	Pattern recognition	• **β (95% CL): 0.074 (0.032), p=0.02***
		Vocabulary	• **β (95% CL): -0.841 (0.20), p=0.0001***
		Word list memory	• **β (95% CL): -0.182 (0.086), p=0.036***
		Boston naming test	• **β (95% CL): -0.036 (0.016), p=0.028***
		Verbal fluency	• β (95% CL): -0.230 (0.120), p=0.09
Power et al. 2014 Longitudinal study, n=584 adult females, mean age 61 years	Mean (SD): • 2.9 (1.9) Tibia Pb (µg/g): Mean (SD): • 10.5 (9.7) Patella Pb (µg/g) mean (SD): • 12.6 (11.7)	Overall cognition	β for 1-age year change in score per 1 SD PbB: -0.013 (-0.044, 0.017)
		Verbal memory	β for 1-age year change in score per 1 SD PbB: 0.006 (-0.037, 0.050)
Seo et al. 2014 Cross-sectional study, n=31 retired female Pb workers, mean age 60.4 years, and 34 controls	Gmean (range): Exposed: 4.07 (0.88–13.5) Controls: 2.00 (1.24–6.47)	Verbal memory	Accuracy % (SD), exposed versus control: • 1-back test: 55.9 (19.8) versus 65.4 (19.4), p=0.056 • **2-back test: 61.4 (20.1) versus 77.2 (15.6), p=0.001***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Shih et al. 2006 Cross-sectional study, n=985 adults, mean age 59.4 years	Mean (SD): • 3.46 (2.23) Tibia Pb (µg/g) mean (SD): • 18.72 (11.24)	Language	• **B per 1 µg/g tibia Pb: -0.0083 (0.0023), p≤0.01***
		Processing speed	• **β per 1 µg/g tibia Pb: -0.0042 (0.0021), p<0.01***
		Eye-hand	• **β per 1 µg/g tibia Pb: -0.0079 (0.0020), p≤0.01***
		Executive function	• **β per 1 µg/g tibia Pb: -0.0075 (0.0019), p≤0.01***
		Verbal memory and learning	• **β per 1 µg/g tibia Pb: -0.0078 (0.0024), p≤0.01***
		Visual memory	• **β per 1 µg/g tibia Pb: -0.0067 (0.0023), p≤0.01***
		Visuoconstruction	• **β per 1 µg/g tibia Pb: -0.0122 (0.0027), p≤0.01***
Weisskopf et al. 2007 Longitudinal study cohort, n=1,089 males, mean age 68.7 years	Median (IQ range): • 5 (3–6) Tibia Pb (µg/g) median (IQ range): • 20 (13–28) Patella Pb (µg/g) median (IQ range): • 25 (17–37)	Vocabulary	**β per 3 µg/dL increase in PbB: -1.26 (-2.08, -0.44), p=0.003***
		Visuoconstruction (patella Pb)	**β per IQR: -0.067 (-0.11, -0.02), p=0.0041***
		Pattern comparison latency (tibia Pb)	**β: 0.079 (0.04, 0.12), p=0.0004***
Weuve et al. 2006 Longitudinal study cohort, n=915 males, mean age 68.7 years	Median (IQ range): • 5.2 (2.9) • 94% <10	Cognitive function	Change in MMSE score per IQR in PbB, 3 µg/dL: • **ALAD-2: IQR (95% CL): -0.29 (-0.56, -0.02)*** • ALAD wildtype: IQR (95% CL): -0.05 (-0.16, 0.06)

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Weuve et al. 2009 Longitudinal study cohort, n=587 females, mean age 61 years	Mean (SD): • 2.9 (1.9) Tibia Pb (µg/g) median (SD): • 10.5 (9.7) Patella Pb (µg/g) median (SD): • 12.6 (11.6)	Cognitive function	Change in score per 1 SD in PbB or bone Pb: • PbB: -0.016 (-0.071, 0.039), p=0.57 • **Tibia: -0.051 (-0.099, -0.003), p=0.04*** • Patella Pb: -0.033 (-0.080, 0.014), p=0.17
Wright et al. 2003b Longitudinal study cohort, n=736 males, mean age 68.2 years	Mean (SD): • All: 4.5 (2.5) • Q1: 2.5 • Q2: 4.0 • Q3: 5.9 • Q4: 8.9 Tibia Pb (µg/g) median (SD): • 22.4 (15.3) Patella Pb (µg/g) median (SD): • 29.5 (21.2)	MMSE score	Adjusted OR with 1 µg/dL increase in PbB or 1 µg/g increase in bone Pb: • **PbB: 1.21 (1.07, 1.36)*** • **Patella Pb: 1.02 (1.00, 1.03)*** • **Tibia Pb: 1.02 (1.00, 1.04)*** Effect of age increased with increasing PbB. β for age with increasing Pb for PbB quartile (95% CL): • **Q1 -0.04 (-0.07, -0.02)*** • **Q2 -0.04 (-0.08, -0.01)*** • **Q3 -0.09 (-0.13, -0.06)*** • **Q4 -0.12 (-0.17, -0.02)***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Mood and behavior			
Bouchard et al. 2009 Cross-sectional study, n=1,987 adults (age 20–39 years)	Gmean±GSD (range): • 1.24 (1.96) • 99%≤10 • Q1: 0.6 • Q2: 0.9 • Q3: 1.2 • Q4: 1.3 • Q5: 3.0	Major depressive disorder	• **Adjusted ORs for PbB for Q5 relative to Q1: 2.32 (1.13, 4.75); p-trend=0.05*** • **Eliminating current smokers, adjusted ORs for PbB for Q5 relative to Q1: 2.93 (1.24, 6.92); p-trend=0.03***
		Panic disorder	• **Adjusted ORs for PbB for Q5 relative to Q1: 4.94 (1.32, 18.48); p-trend=0.02*** • **Eliminating current smokers, adjusted ORs for PbB for Q5 relative to Q1: 9.57 (1.28, 71.43); p-trend=0.01***
		Generalized anxiety disorder	• Adjusted ORs for PbB for Q5 relative to Q1: 1.53 (0.39, 5.96); p-trend=0.78 • Eliminating current smokers, adjusted ORs for PbB for Q5 relative to Q1: 1.59 (0.19, 13.31); p-trend=0.44
Buser and Scinicariello 2017 Cross-sectional study of 3,905 adults (age ≥20 years) from NHANES 2011–2012	Cohort stratified into PbB quartiles: • Q1: <0.7 • Q2: 0.70–1.06 • Q3: 1.07–1.67 • Q4: >1.67	Depression	Adjusted OR for depression symptoms in adult females (age 20–47 years) associated with increasing PbB: • **Q3: 1.86 (1.01, 3.41, p<0.05*** • **Q4: 2.97 (1.01, 8.74), p<0.05***
Golub et al. 2010 Cross-sectional study of 4,195 adults (age ≥20 years) from NHANES 2005–2006	Cohort stratified into PbB quartiles: • Q1: <0.88 • Q2: 0.89–1.40 • Q3: 1.41–2.17 • Q4: 2.18–26.4		Adjusted OR for depression symptoms was elevated in PbB quartile 3 (95% CI): • **Q3: 1.25 (1.07, 1.47)***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Opler et al. 2004 Case-control study, n=44 schizophrenia cases and 75 matched controls from birth cohorts	Cohort stratified into <15 or ≥15 µg/dL based on 2nd trimester ALA measurements	Schizophrenia	Adjusted OR for schizophrenia associated with high (≥15 µg/dL) prenatal PbB: 2.43 (0.99, 5.96), p=0.051
Opler et al. 2008 Case-control study, n=71 schizophrenia cases and 129 matched controls	Cohort stratified into <15 or ≥15 µg/dL based on 2nd trimester ALA measurements	Schizophrenia	Adjusted OR for schizophrenia associated with high (≥15 µg/dL) prenatal PbB: **1.92 (1.05, 3.87), p=0.03***
Rajan et al. 2007 Longitudinal study cohort, n=1,075 males, mean age 67.1 years	Mean (SD): • All: 6.2 (4.1) Tibia Pb (µg/g) median (SD): • 22.1 (13.8) Patella Pb (µg/g) median (SD): • 31.4 (19.6)	Somatization, tibia Pb	Adjusted OR for inter quartile increases in tibia Pb (14 µg/g) or patella Pb (20 µg/g): **1.21 (1.01, 1.46)***
		Global severity index, patella Pb	**OR: 1.23 (1.02, 1.47)***
Rhodes et al. 2003 Longitudinal study cohort, n=526 males, mean age 67.1 years	Mean (SD): • 6.3 (4.2) Tibia Pb (µg/g) median (SD): • 21.9 (13.5) Patella Pb (µg/g) median (SD): • 32.1 (19.8)	Phobic anxiety	**Adjusted OR (95% CL) for inter quintile increases in patella Pb (8.9 µg/dL: 1.91 (1.01, 3.61)***
		Combined symptoms	**Adjusted OR (95% CL) for inter quintile increases** • **PbB OR: 2.91 (1.39, 6.09)*** • **Tibia Pb OR: 2.08 (1.06, 4.07)*** • **Patella Pb OR: 3.62 (1.62, 8.08)***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Scinicariello and Buser 2015 Cross-sectional study of 2,892 adults (age 20–39 years) from NHANES 2007–2010	**PbB:** Gmean (GSD) • 0.96 (0.02).	Depression	Adjusted OR for depression symptoms was not associated with increasing PbB (ORs were not reported).
Neuromotor neurosensory function			
Hwang et al. 2009 Cross-sectional study, n=259 male steel workers, mean age 36.0 years	Mean (SD): 5.43 (3.46)	Hearing loss	Adjusted OR for hearing loss (>25 dB) at 3,000–8,000 Hz in PbB categories relative to ≤4 µg/dL: Loss at 3000 Hz • 4–7 µg/dL: 0.75 (0.17, 3.29) • **≥7 µg/dL: 4.49 (1.28, 15.8); p<0.005*** Loss at 4000 Hz: • **4–7 µg/dL: 3.54 (1.40, 8.97)*** (p-value not reported) • **≥7 µg/dL: 6.26 (2.35, 16.6); p<0.005*** Loss at 6000 Hz: • 4–7 µg/dL: 2.11 (0.94, 4.47) • **≥7 µg/dL: 3.06 (1.27, 7.39); p<0.05***
Ji et al. 2013 Cross-sectional study, n=1,795 males and 1,798 females, age >50 years (median 61.2)	Mean (SD): • Females: 2.17 (0.06) • Males: 3.18 (0.12)	Walking speed	Mean change in walking speed (ft/sec) for PbB quintile relative to Q1 (≤1.2 µg/dL): • PbB 1.3–≤1.6. β: -0.024 (-0.112, 0.064), p=0.58 • PbB 1.7–≤2.1, β: -0.027 (-0.118, 0.063), p=0.54 • **PbB 2.2–≤2.9, β: -0.104 (-0.187, -0.021), p=0.02*** • **PbB 3.3–≤53.0, β: -0.114 (-0.191, -0.038), p=0.01*** • **P-trend=0.005***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Ji et al. 2015 Longitudinal study cohort, n=807 males, mean age 69 years	Mean (SD): 5.0 (2.7) • % <10: 96% Bone Pb, µg/g (SD) • Patella: 28.0 (18.4) Tibia: 21.2 (13.3)	Tremor	OR for tremor by PbB quintile (95% CL): • Q5 (8–28), PbB: 0.84 (0.38, 1.86), p=0.72 • Q5 (40–165), patella Pb: 0.83 (0.31, 2.19), p=0.41 • Q5 (30–126): tibia Pb: 1.08 (0.46, 2.53), p=0.60
Muldoon et al. 1996 Cross-sectional study, n=530 adult women, mean age 70 years	Mean (SD): • All: 4.8 (0.4) • Rural: 4.5 (0.4) • Urban: 5.4 (0.4) • Low: <4 • Medium: 4–7 • High: >7	Pegboard	OR for poor performance (low PbB reference) in the rural cohort: ANOVA, p=0.98 • Medium PbB: OR (95% CL): 1.37 (0.71, 2.65) • High PbB: OR (95% CL): 1.16 (0.45, 3.01)
		Upper extremity	ANOVA, p<0.01, in the rural cohort • Medium PbB: OR (95% CL): 1.39 (0.73, 2.65) • **High PbB: OR (95% CL): 2.43 (1.01, 5.83)***
		Lower extremity	ANOVA, p<0.01, in the rural cohort • Medium PbB: OR (95% CL): 1.29 (0.68, 2.47 • **High PbB: OR (95% CL): 2.84 (1.19, 6.74)***
Neurological disease			
Fang et al. 2010 Case-control study, n=184 male ALS cases and 194 matched controls, mean age 63 years	Mean (range): • Controls: 1.76 (0.32–6.90) • Cases: 2.41 (0.72–7.58)	ALS	**Adjusted OR for ALS for doubling of PbB:** • **All cases (n=184): 1.9 (1.3, 2.7)*** • **Excluding progressive muscular atrophy and primary lateral sclerosis (n=151): 1.8 (1.2, 2.5)***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Kamel et al. 2002 Case-control study, n=109 ALS cases and 256 matched controls, age 30–80 years	Mean (range): • Cases: 3 of 194 had PbB >10 • Controls: <10 µg/dL	ALS	• Adjusted OR for ALS (for a 1 µg/dL increase in PbB: **1.9 (1.4, 2.6)*** • Adjusted OR for ALS relative to <2 µg/dL: ○ **3–4 µg/dL: 14.3 (3.0, 69.3)*** ○ **5–14 µg/dL: 24.5 (4.3, 139.3)***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 10 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Asterick indicates association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.

ALA = aminolevulinic acid; ALAD-2 = delta-aminolevulinic acid dehydratase allele; ALS = amyotrophic lateral sclerosis; ANOVA = analysis of variance; CI = confidence interval; CL = confidence limit; Gmean = geometric mean; GSD = geometric standard deviation; IQ = intelligence quotient; IQR = interquartile range; MMSE = Mini-Mental Status Examination; OR = odds ratio; Pb = lead; RR = relative risk; SD = standard deviation; SE = standard error

Altered neuromotor neurosensory function. Several studies have examined associations between Pb exposure assessed from blood or bone Pb and performance on tests of neuromotor or neurosensory function (Table 2-32). The largest study analyzed data from NHANES III (1988–1994) and found no association (p=0.34) between concurrent PbB and simple visual reaction time in a cohort of 5,700 adults (age 20–50 years; Krieg et al. 2005). The geometric mean PbB was 2.51 μg/dL (range 0.7–42) and 96% of the cohort was <10 μg/dL. A more recent analysis of data from NHANES (1999–2002) examined walking speed in cohorts of approximately 1,800 males or females and found a significant association between increasing PbB and decreasing walking speed in females in a PbB stratum 2.2–≤2.9 μg/dL compared to 1.6 μg/dL; there was a significant trend with increasing PbB (Ji et al. 2013). This outcome is consistent with a smaller cross-sectional study of women (mean age 70±4 years) that found significant decreases in upper and lower extremity reaction times in association with increasing PbB (Muldoon et al. 1996). A longitudinal study of a cohort from the Normative Aging Study found no significant associations between bone or blood Pb and hand tremor in males (mean age 60±7 years; Ji et al. 2015). The mean PbB for the cohort was 5.0±2.7 (SD) μg/dL.

Neurological diseases. Possible associations between Pb exposure and risk of ALS have been examined in case-control studies (Fang et al. 2010; Kamel et al. 2002). A case-control study of 184 male ALS cases and 194 matched controls found a significant association between increasing PbB and ALS (Fang et al. 2010). The mean PbB for cases was 2.41 μg/dL (range 0.72–7.58 μg/dL). A case-control study of 109 ALS cases (43 females, 66 males) and 194 matched controls estimated the OR for ALS to be 1.9 (95% CL 1.4, 2.6) for a 1 μg/dL increase in PbB (Kamel et al. 2002).

Associations Between Bone Pb and Neurological Effects in Adults. Decrements in neurological function in adults have also been associated with bone Pb (Table 2-33). In general, these studies provide further support for associations between Pb exposure and neurobehavioral function, including decrements in cognitive function, altered neuromotor and neurosensory function, and altered behavior and mood. Most of these studies are of cohorts from longitudinal health studies: Boston Memory Study (Bandeen-Roche et al. 2009; Glass et al. 2009; Shih et al. 2006), Nurses' Health Study (Power et al. 2014; Weuve et al. 2009), or Normative Aging Study (Eum et al. 2013; Grashow et al. 2013a, 2013b, 2015; Ji et al. 2015; Park et al. 2010; Payton et al. 1998; Power et al. 2014; Rajan et al. 2007, 2008; Rhodes et al. 2003; Schwartz et al. 2005; Wang et al. 2007; Weisskopf et al. 2004, 2007; Wright et al. 2003b). These studies have provided both cross-sectional and longitudinal assessments of associations between bone Pb (and PbB) and neurological function in adult populations. Longitudinal designs are particularly important because they allow age-related declines in cognitive function to be assessed. Longitudinal studies have

found that associations between bone Pb and cognitive function (learning, memory) persist when adjustments are made for age (Bandeen-Roche et al. 2009; Dorsey et al. 2006; Eum et al. 2013; Grashow et al. 2013a; Khalil et al. 2009; Payton et al. 1998; Power et al. 2014; Rajan et al. 2008; Schwartz et al. 2005; Seegal et al. 2013; Shih et al. 2006; Stewart et al. 2002; van Wijngaarden et al. 2009; Weisskopf et al. 2007; Weuve et al. 2009, 2013; Wright et al. 2003b). Rates of decrement in cognitive function with age have been found to be more severe in association with increasing bone Pb (Power et al. 2014; Schwartz et al. 2005; Wang et al. 2007; Weisskopf et al. 2004, 2007; Wright et al. 2003b).

Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

		Neurological outcome			
Reference	Population	Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Bandeen-Roche et al. 2009	965 adults, age: 50–70 years[a]	↑ T	–	–	Learning, memory, executive function, eye-hand coordination
Coon et al. 2006	121 adult cases, 414 controls, age: 50–>80 years	–	↑ 0[d]	–	Parkinson's disease
Dorsey et al. 2006	652 adult lead workers, age: 20–70 years	↑ P ↑ T	↑ P ↑ T	↑ P ↑ T	Reaction time, executive function. manual dexterity, vibration threshold, depression
Eum et al. 2013	789 adult males[b], age: 68 years (median)	↑ P ↑ T	–	–	Memory, verbal and written skills, executive function
Eum et al. 2015	100 adult cases, 194 controls, age: 60 years (mean)	–	↑ P ↑ T	–	Interaction between lead, amyotrophic lateral sclerosis and hemochromatosis gene polymorphisms

Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

		Neurological outcome			
Reference	Population	Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Glass et al. 2009	1,001 adults[a], age: 50–70 years	↑ T	↑ T	–	Interaction between lead and psychosocial hazard scale for eye-hand coordination, executive function, language
Grashow et al. 2013a	51 adult males[b], age: 75 years (mean)	↑ P 0 T	–	–	Fear conditioning
Grashow et al. 2013b	362 adult males[b], age: 69 years (mean)	–	↑ P ↑ T	–	Manual dexterity
Grashow et al. 2015	164 adult males[b], age: 80 years (mean)	–	0 P ↑ T	–	Olfactory function
Ji et al. 2015	672 adult males[b], age: 50–98 years	–	0 P 0 T	–	Tremor (no association in adjusted models)
Kamel et al. 2002	109 adult cases, 256 controls, age: 30–80 years	–	0 P 0 T	–	Amyotrophic lateral sclerosis (no association in adjusted models)
Khalil et al. 2009	83 adult workers and 51 controls, age: >55 years	↑ T	–	–	Learning, memory
Park et al. 2010	448 adult males[b], age: 65 years (mean)	–	↑ P ↑ T	–	Hearing function
Payton et al. 1998	141 adult males[b], age: 67 years (mean)	↑ T	–	–	Memory, visual-spatial performance
Power et al. 2014	584 adult females[c], age: 60–74 years	0 P 0 T	–	–	Learning, memory, executive function
Rajan et al. 2007	1,075 adult males[b], age: 48–94 years	–	–	↑ P ↑ T	Psychiatric symptoms

Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

		Neurological outcome			
Reference	Population	Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Rajan et al. 2008	982 adult males[b], age: 49–>72 years	0 P ↑ T	–	–	Visual-spatial performance
Rhodes et al. 2003	536 adult males[b], age: 48–70 years	–	–	↑ P ↑ T	Anxiety
Schwartz et al. 2000b	535 lead workers, age: 56 years (mean)	↑ T	↑ T	–	Memory, executive function, manual dexterity
Schwartz et al. 2001	803 exposed lead workers and 135 controls, age: 40 years (mean)	0 T	0 T	0 T	Learning, memory, executive function, manual dexterity, grip strength, mood and depression
Schwartz et al. 2005	576 exposed lead workers, age: 41 years (mean)	↑ T	↑ T	↑ T	Executive function, manual dexterity, vibration threshold, depression
Seegal et al. 2013	241 capacitor workers, age: 64 years (mean)	↑ T	↑ T	–	Learning, memory, executive function, manual dexterity
Shih et al. 2006	991 adults[a], age: 50–70 years	↑ T	↑ T	–	Learning, memory, executive function, manual dexterity
Stewart et al. 2002	529 lead workers, age: 40–>70 years	↑ T	↑ T	–	Learning, memory, executive function, reaction time, manual dexterity
van Wijngaarden et al. 2009	47 adults, age: 55–67 years	↑ C	–	–	Learning, memory
Wang et al. 2007	358 adult males[b], age: 67 years (median)	↑ T	–	–	Interaction between lead and hemochromatosis gene polymorphisms on learning, memory, executive function

Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

		Neurological outcome			
Reference	Population	Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Weisskopf et al. 2004	466 adult males[b], age: 68 years (mean)	↑ P	–	–	Memory, verbal and written skills, executive function
Weisskopf et al. 2007	761 adult males[b], age: 69 years (mean)	↑ P ↑ T	–	–	Memory, visual-spatial performance
Weisskopf et al. 2010	330 adult cases and 308 controls, age: 67 years (mean)	–	↑ T	–	Parkinson's disease
Weuve et al. 2009	587 adult females[c], age: 47–74 years	0 P ↑ T	–	–	Learning, memory
Weuve et al. 2013	101 cases and 50 controls, age: 55–80 years	0 P ↑ T	–	–	Learning, memory (stronger association with lead among Parkinson's disease cases)
Wright et al. 2003b	736 adult males[b], age: 68 years (mean)	↑ P ↑ T	–	–	Memory, verbal and written skills, executive function

[a]Boston Memory Study.
[b]Normative Aging Study.
[c]Nurses Health Study.
[d]Whole-body lead predicted from bone lead.

↑ = positive association; ↓ = negative association; 0 = no association; – = not reported; C = calcaneous bone; P = patella; Pb = lead; T = tibia; O = other

Bone Pb has been associated with declines in neuromotor and neurosensory function. Neuromotor outcomes that have been associated with bone Pb include tremor, Parkinson's disease, and ALS (Coon et al. 2006; Eum et al. 2015; Weisskopf et al. 2010; Weuve et al. 2013). Neurosensory outcomes include decrements in olfactory and hearing function, vibration threshold, and manual dexterity (Dorsey et al. 2006; Grashow et al. 2013b, 2015; Park et al. 2010; Schwartz et al. 2000b; 2005; Shih et al. 2006; Stewart et al. 2002). Bone Pb has also been associated with increased risk or odds of psychiatric symptoms such

as anxiety and depression (Dorsey et al. 2006; Rajan et al. 2007; Rhodes et al. 2003; Schwartz et al. 2005).

Mechanisms of Action. Pb disrupts cellular function through diverse mechanisms, including displacement of metal ion co-factors from protein, enzyme inhibition, inhibition of ion transport, disruption of cell and mitochondrial membrane potentials, disruption of intracellular calcium homeostasis oxidative stress, and inflammation and endocrine disruption (see Section 2.21). All of these Pb mechanisms have been demonstrated in neuronal tissues, although there is no consensus on which mechanisms dominate. Evidence for various mechanisms that may participate in Pb neurotoxicity are summarized in this section. The reader is referred to references cited therein for more detailed information (Bouton and Pevsner 2000; Bressler et al. 1999; Cory-Slechta 1995, 2003; EPA 2014c; Gilbert and Lasley 2002; Lasley and Gilbert 2000; Nihei and Guilarte 2002; Suszkiw 2004; Toscano and Guilarte 2005; Zawia et al. 2000; Zhang et al. 2015).

Pb can affect the nervous system by multiple mechanisms, one of the most important of which is by mimicking calcium action and/or disruption of calcium homeostasis. Because calcium is involved as a cofactor in many cellular processes, it is not surprising that many cell-signaling pathways are affected by Pb. One pathway that has been studied in more detail is the activation of protein kinase C (PKC). PKC is a serine/threonine protein kinase involved in many processes important for synaptic transmission such as the synthesis of neurotransmitters, ligand-receptor interactions, conductance of ionic channels, and dendritic branching. The PKC family is made up of 12 isozymes, each with different enzymatic cofactor requirements, tissue expression, and cellular distributions. The γ-isoform is one of several calcium-dependent forms of PKC and is a likely target for Pb neurotoxicity; it is neuron-specific and is involved in long-term potentiation (see below), spatial learning, and memory processes. Pb has the capacity to both activate and inhibit PKCs. Studies have shown that micromolar concentrations of Pb can activate PKC-dependent phosphorylation in cultured brain microvessels, whereas picomolar concentrations of Pb activate preparations of PKC *in vitro*. Interestingly, studies in rats exposed to low Pb levels have shown few significant changes in PKC activity or expression, suggesting that the whole animal may be able to compensate for Pb PKC-mediated effects compared to a system *in vitro*. PKC induces the formation of the AP-1 transcriptional regulatory complex, which regulates the expression of a large number of target genes via AP-1 promoter elements. A gene regulated by Pb via AP-1 promoters is the glial fibrillary acidic protein (GFAP), an astrocytic intermediate filament protein that is induced during periods of reactive astrocytic gliosis. Astrocytes, along with endothelial cells, make up the blood-brain barrier. Studies in rats exposed chronically to low Pb levels have reported alterations in the normal pattern of

GFAP gene expression in the brain, and the most marked long-lasting effects occurred when the rats were exposed during the developmental period. In immature brain microvessels, most of the protein kinase C is in the cytosol, whereas in mature brain microvessels, this enzyme is membrane-bound. Activation of protein kinase C in other systems is known to result in a change in distribution from cytosol to membrane, and has been observed with exposure of immature brain microvessels to Pb. An inhibition of microvascular formation has been observed with Pb concentrations that are effective in activating PKC. Thus, it appears that premature activation of PKC by Pb may impair brain microvascular formation and function, and at high levels of Pb exposure, may account for gross defects in the blood-brain barrier that contribute to acute Pb encephalopathy. The blood-brain barrier normally excludes plasma proteins and many organic molecules, and limits the passage of ions. With disruption of this barrier, molecules such as albumin freely enter the brain, and ions and water follow. Because the brain lacks a well-developed lymphatic system, clearance of plasma constituents is slow, edema occurs, and intracranial pressure rises. The particular vulnerability of the fetus and infant to the neurotoxicity of Pb may be due in part to immature brain microvessels, which affect the blood brain barrier, and to the lack of the high-affinity Pb-binding protein in astroglia, which sequester Pb.

Another enzyme altered by Pb is calmodulin, a major intracellular receptor for calcium in eukaryotes. Normally, calcium induces a conformational change in calmodulin that converts the protein to an active form; Pb improperly activates the enzyme. Some studies suggest that activation of calmodulin by Pb results in protein phosphorylation in the rat brain and brain membrane preparations and can alter proper functioning of cAMP messenger pathways. It has been shown that calmodulin can mediate gene expression via calmodulin-dependent kinases. The effects of Pb on gene expression via activation of calmodulin are not as marked as those via PKC because activation of calmodulin requires 100-fold more Pb than activation of PKC.

Pb also can substitute for zinc in some enzymes and in zinc-finger proteins, which coordinate one or more zinc cations as cofactors. The substitution of Pb for zinc in zinc-finger proteins can have significant effects on *de novo* expression of the bound proteins and in any genes transcriptionally-regulated by a particular protein. Pb has been found to alter the binding of zinc-finger transcriptional regulator Sp1 to its specific DNA sequences. This is accompanied by aberrant expression of Sp1 target genes such as myelin basic protein and proteolipid protein. Another gene regulated by Sp1 is the β-amyloid precursor protein (APP) gene. Recently, it was shown that Pb exposure in neonatal rats transiently induces APP mRNA, which is overexpressed with a delay of 20 months after exposure to Pb has ceased. In contrast, APP expression, and Sp1 activity, as well as APP and β-amyloid protein levels, were unresponsive to Pb

during old age, suggesting that exposures occurring during brain development may predetermine the expression and regulation of APP later in life. It has been suggested that the multiple responses to Pb exposure are due to Pb specifically targeting zinc-finger proteins found in enzymes, channels, and receptors.

Pb affects virtually every neurotransmitter system in the brain, but most information on changes is available on the glutamatergic, dopaminergic, cholinergic, and gamma-aminobutyric acid (GABA). Of these, special attention has been paid to the glutamatergic system and its role in hippocampal long-term potentiation (LTP). Hippocampal LTP is a cellular model of learning and memory characterized by a persistent increase in synaptic efficacy following delivery of brief tetanic stimulation (high-frequency stimulation). LTP provides a neurophysiological substrate for learning and storing information and is thought to utilize the same synaptic mechanisms as the learning process. LTP is established only with complex patterns of stimulation but not with single pulse stimulation. While it has been studied primarily in the hippocampal subregions CA1 and dentate gyrus, it can also be evoked in cortical areas. Exposure of intact animals or tissue slices to Pb diminishes LTP by a combination of three actions: increasing the threshold for induction, reducing the magnitude of potentiation, and shortening its duration by accelerating its rate of decay. This effect on LTP involves actions of Pb on glutamate release (presynaptic effects) and on the N-methyl-D-aspartate (NMDA) receptor function. Pb exposure inhibits release of glutamine from pre-synaptic endings, which may be mediated, in part, by altered pre-synaptic vesicle formation or activation. Studies have shown that the effects of Pb vary as a function of the developmental exposure period and that Pb exposure early in life is critical for production of impaired LTP in adult animals. LTP is more readily affected by Pb during early development, but exposure initiated after weaning also affects synaptic plasticity. Studies also have shown that both LTP magnitude and threshold exhibit a U-shape type response with increasing Pb doses. While LTP is primarily a glutamatergic phenomenon, it can be modulated through input from extrahippocampal sources including noradrenergic, dopaminergic, and cholinergic sources.

Studies in animals treated with Pb (PbB 30–40 μg/dL) have shown that induction of pair-pulse facilitation in the dentate gyrus is impaired. Since the phenomenon is mediated primarily by increased glutamate release, the reasonable assumption is that Pb reduces glutamate release. Support for this assumption is also derived from studies in which depolarization-induced hippocampal glutamate release was reduced in awake animals with similar PbB. This inhibition of glutamate release was shown to be due to Pb-related decrements in a calcium-dependent component. The exact mechanism for the inhibition of glutamate release by Pb is not known, but is consistent with Pb at nanomolar concentrations preventing maximal

activation of PKC, rather than Pb blocking calcium influx into the presynaptic terminal through voltage-gated calcium channels. Reduced glutamate release can be observed in rats exposed from conception through weaning and tested as adults, when Pb was no longer present, suggesting that a direct action of Pb is not necessary and that other mechanisms, such as reductions in synaptogenesis, also may be involved. As with LTP, depolarization-evoked hippocampal glutamate release in rats treated chronically with several dose levels of Pb exhibited a U-shaped response. That is, glutamate release was inhibited in rats treated with the lower Pb doses, but not in those exposed to the higher concentrations of Pb. Although speculative, this was interpreted as Pb at the higher doses mimicking calcium in promoting transmitter release and overriding the inhibitory effects of Pb that occur at lower Pb levels.

The findings regarding the effects of Pb on postsynaptic glutamatergic function have been inconsistent across laboratories, but a direct inhibitory action of Pb on the NMDA receptor is unlikely at environmentally relevant exposure levels. Some studies have shown that continuous exposure of rats from gestation to adulthood results in a significant increase in NMDA receptor numbers in cortical areas, hippocampus, and forebrain. This was observed in the forebrain at PbB of 14 μg/dL. Other studies, however, have reported changes in the opposite direction and the reason for the discrepancy in results may be due to the different exposure protocols used. From a functional point of view, it seems plausible that a Pb-induced reduction in presynaptic transmitter release be compensated by a postsynaptic increase in number or density of receptors in order to maintain a viable function.

The dopaminergic system also has a role in aspects of cognitive function since lesions of dopaminergic neurons impair behavior in various types of learning and cognitive tasks. Also, individuals who suffer from Parkinson's disease, a disease associated with dopamine depletion in the striatum, sometimes show difficulties in cognitive functions. Most of the evidence available suggests that Pb may impair regulation of dopamine synthesis and release, indicating a presynaptic site of action. Studies in animals often report opposing effects of Pb on nigrostriatal and mesolimbic dopamine systems regarding receptor binding, dopamine synthesis, turnover, and uptake. Postweaning exposure of rats to Pb resulted in supersensitivity of D1 and D2 dopamine receptors, which can be interpreted as a compensatory response to decreased synthesis and/or release of dopamine. Lesions to the nucleus accumbens (a terminal dopamine projection area) and the frontal cortex result in perseverative deficits, suggesting that the mesolimbic system is preferentially involved in the effects of Pb. Results of studies using dopaminergic compounds seem to indicate that changes in dopamine systems do not play a role in the effects of Pb on learning. Instead, it has been suggested that changes in dopaminergic systems may play a role in the altered response rates on

Fixed-Interval (FI) schedules of reinforcement that have been observed in animals exposed to Pb. This type of change has been thought to represent a failure to inhibit inappropriate responding.

It is widely accepted that the cholinergic system plays a role in learning and memory processes. Some cognitive deficits observed in patients with Alzheimer's disease have been attributed to impaired cholinergic function in the cortex and hippocampus. Exposure to Pb induces numerous changes in cholinergic system function, but the results, in general, have been inconsistently detected, or are of opposite direction in different studies, which may be attributed to the different exposure protocols used in the different studies. However, it is clear that Pb blocks evoked release of acetylcholine and diminishes cholinergic function. This has been demonstrated in central and peripheral synapses. Studies with the neuromuscular junction showed that Pb reduces acetylcholine release by blocking calcium entry into the terminal. At the same time, Pb prevents sequestration of intracellular calcium by organelles, which results in increased spontaneous release of the neurotransmitter. Studies *in vitro* show that Pb can block nicotinic cholinergic receptors, but it is unclear whether such effects occur *in vivo* or whether Pb alters the expression of nicotinic cholinergic receptors in the developing brain. Evidence for an involvement in Pb-induced behavioral deficits has been presented based on the observation that intrahippocampal transplants of cholinergic-rich septal and nucleus basalis tissue improve the deficits and that treatment with nicotinic agonists can improve learning and memory impairments following perinatal Pb treatment of rats. Chronic exposure of rats to Pb has resulted in decreased muscarinic-receptor expression in the hippocampus. Whether or not Pb exposure during development alters muscarinic receptor sensitivity is unclear as there are reports with opposite results. The preponderance of the binding data suggests that Pb does not directly affect muscarinic receptors with the exception of the visual cortex, where Pb may have a direct inhibitory effect on muscarinic receptors from rods and bipolar cells of the retina.

Pb exposure decreases spontaneous and evoked release of GABA in rats and in hippocampal cultures and brain slices. In general, GABA functions in the brain as a post-synaptic inhibitory transmitter. The role of changes in GABA release in the neurotoxicity of Pb has not been firmly established.

Various other mechanisms may also contribute to Pb neurotoxicity. Exposure to Pb has also been shown to stimulate inflammation in a variety of tissues, including neuronal tissue (see Section 2.21). Contributing mechanisms include alterations in levels of ROS, activation of nuclear activation factor NF6β, cytokine release, and alterations in prostaglandin metabolism. Pb exposure has been shown to alter neuronal nitric oxide signaling (NOS) and the hormone levels regulated by the hypothalamic-pituitary-thyroid axis.

2.17 REPRODUCTIVE

Overview. Numerous epidemiological studies have evaluated effects of Pb on male and female reproductive function. In males, most exposures were occupational, with mean PbB >10 μg/dL. In general, studies in males show consistent evidence of reproductive effects on sperm (production, motility, viability, and morphology), semen quantity and composition, serum reproductive hormone levels, and fertility, with severity of effects increasing with increasing PbB. In contrast to exposure of males, most exposures of females were non-occupational, with mean PbB ≤10 μg/dL. Studies investigating effects on serum reproductive hormone levels, fertility, spontaneous abortion, and preterm birth provide mixed results; thus, dose-dependence of effects in females is difficult to assess.

The following reproductive effects in males have been associated with PbB:

- ≤10 μg/dL:
    - Increased serum testosterone; evaluated in a few studies with mixed results.
    - Effects on sperm (decreased sperm count, concentration, motility, and viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm); evaluated in a few studies with mixed results.
- >10 μg/dL:
    - Altered serum concentrations of reproductive hormones (testosterone, FSH, LH); evaluated in a several studies with mixed results.
    - Effects on sperm (decreased sperm count, concentration, motility, and viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm); corroborated in several studies.
    - Alterations in semen quality (decreased semen volume and altered composition of seminal fluid); evaluated in a few studies.
    - Decreased fertility; evaluated in a few studies.
    - Histopathological changes to the testes (peritubular fibrosis, oligospermia, and vacuolization of Sertoli cells); evaluated in a few studies.

The following reproductive effects in females have been associated with PbB:

- ≤10 μg/dL:
  - Increased serum levels of estradiol, FSH, and LH; studies have mixed results.
  - Decreased fertility; studies have mixed results.
  - Increased spontaneous abortion; studies have mixed results.
  - Increased preterm birth; studies have mixed results.
  - Decreased age at onset of menopause; demonstrated in a few studies.
- >10 μg/dL:
  - Decreased fertility; studies have mixed results.
  - Increased preterm birth; studies have mixed results.

Measures of Exposure. Most studies evaluating effects on male and female reproductive systems used PbB as the biomarker for exposure. More recent studies in men have explored the relationship between the concentration of Pb in semen or spermatozoa and adverse effects (Table 2-34). It has been suggested that semen levels of Pb may be a better biomarker for assessment of male reproductive effects, particularly at low PbB, because no relationship between PbB and Pb levels in semen or spermatozoa has been observed (Hernandez-Ochoa et al. 2005; Mendiola et al. 2011). In women, other biomarkers of exposure include concentration of Pb in plasma (Lamadrid-Figueroa et al. 2007), red blood cells (Perkins et al. 2014), and placenta (Gundacker et al. 2010), and plasma/blood ratio (Lamadrid-Figueroa et al. 2007).

Confounding Factors. Numerous complicating factors may add uncertainty in the interpretation of studies examining associations between PbB and reproductive effects, including overall health, body weight, nutrition, and SES. Exposures to other substances, including recreational drugs, alcohol, therapeutic agents, industrial chemicals, insecticides, and pesticides, also may affect fertility (Foster and Gray 2008). Some studies examining effects on sperm (discussed below) were conducted on samples obtained at fertility clinics; therefore, other causes for sperm effects could be confounding factors (additional details are provided in the *Supporting Document for Epidemiological Studies for Lead,* Table 11). In addition, because sperm counts can vary by geographical location, it is important that control groups are matched for this variable.

Characterization of Effects in Males. General trends regarding the relationship between PbB and male reproductive effects are shown in Table 2-34. Overall, the dose-effect pattern suggests an increasing

severity of toxicity associated with increasing PbB, with effects on sperm at ≤10 μg/dL (discussed in more detail below). At increasing PbB, effects become more severe, with decreased fertility observed at PbB >10 μg/dL and histopathological changes of the testes at PbB of approximately 30 μg/dL. Effects on sperm, including decreased sperm count, concentration, motility, and viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm, have been observed at PbB of ≤10–>50 μg/dL (Alexander et al. 1998; Assennato et al. 1987; Bonde et al. 2002; Cullen et al. 1984; Hernández-Ochoa et al. 2005; Kasperczyk et al. 2008; Lancranjan et al. 1975; Lerda 1992; Li et al. 2015; Meeker et al. 2008; Moran-Martinez et al. 2013; Telisman et al. 2007; Wildt et al. 1983). However, a few studies showed no association between PbB and adverse effects on sperm (Lancranjan et al. 1975; Mendiola et al. 2011). Decreased semen volume and altered composition of seminal fluid have been observed at PbB >10 μg/dL (Bonde et al. 2002; Naha and Chowdhury 2006; Telisman et al. 2000; Wildt et al. 1983). Decreased fertility has been reported in association with PbB >10–>50 μg/dL (Sallmén et al. 2000b; Shiau et al. 2004), although no effect on fertility was observed in one study of workers with PbB >40 μg/dL (Coste et al. 1991). Histopathological assessment of biopsied testicular tissue from Pb workers (mean PbB 29.0 μg/dL) showed peritubular fibrosis, oligospermia, and vacuolization of Sertoli cells (Braunstein et al. 1978). Evaluations of associations between PbB and serum levels of reproductive hormones show inconsistent results (Table 2-35). At PbB ≤10 μg/dL, positive associations between PbB and serum testosterone levels have been observed (Kresovich et al. 2015; Lewis and Meeker 2015; Meeker et al. 2010; Telisman et al. 2007), whereas negative associations or no effects were reported at PbB >10 μg/dL. No effects on FSH or LH were reported at PbB ≤10 μg/dL, and inconsistent results were observed at PbB >10 μg/dL. Changes in serum levels of reproductive hormones may indicate disruption of the hypothalamic-pituitary-gonadal axis; however, due to inconsistent findings, an association between PbB and endocrine disruption in males has not been firmly established.

Table 2-34. Overview of Effects on the Male Reproductive System Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (μg/dL)	Effects associated with Pb exposure	References
≤10	Effects on sperm (decreased sperm concentration, motility, and viability; increased morphologic abnormalities)	Hernández-Ochoa et al. 2005; Li et al. 2015; Meeker et al. 2008; Telisman et al. 2007
	Effects on hormones (increased serum levels of testosterone and estradiol; decreased serum prolactin and sex-hormone binding globulin)	Kresovich et al. 2015; Lewis and Meeker 2015; Meeker et al. 2010; Telisman et al. 2007

Table 2-34. Overview of Effects on the Male Reproductive System Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
>10–30	Effects on sperm (decreased sperm count, concentration, density, motility, and viability; morphologic abnormalities)	Alexander et al. 1998; Bonde et al. 2002; Moran-Martinez et al. 2013
	Effects on semen (decreased volume)	Bonde et al. 2002
	Decreased fertility	Sallmén et al. 2000b
>30–50	Effects on sperm (decreased count, concentration, motility, viability; morphologic abnormalities)	Hsu et al. 2009; Lancranjan et al. 1975; Lerda 1992; Telisman et al. 2000
	Effects on composition of seminal fluid	Telisman et al. 2000
	Effects on hormones (increased estradiol, LH, FSH; decreased testosterone)	Braunstein et al. 1978; Ng et al. 1991; Telisman et al. 2000
	Histopathological changes to testes (peritubular fibrosis, oligospermia, vacuolization of Sertoli cells)	Braunstein et al. 1978
	Decreased fertility	Sallmén et al. 2000b; Shiau et al. 2004
>50	Effects on sperm (decreased count, concentration, motility, viability; morphologic abnormalities)	Assennato et al. 1987; Cullen et al. 1984; Kasperczyk et al. 2008; Lancranjan et al. 1975; Lerda 1992; Naha and Chowdhury 2006; Wildt et al. 1983
	Effects on semen (decreased volume; altered composition)	Naha and Chowdhury 2006; Wildt et al. 1983
	Effects on hormones (altered serum levels of testosterone, FSH, LH, prolactin)	Assennato et al. 1987; Rodamilans et al. 1988
	Decreased fertility	Sallmén et al. 2000b

FSH = follicle-stimulating hormone; LH = luteinizing hormone

Table 2-35. Effects on Reproductive Hormones Associated with Chronic Exposure to Lead (Pb) in Males

PbB (µg/dL)	Hormone							Reference
	T	FSH	LH	E	P	A	SHBG	
≤10	↑	0	–	–	–	0	0	Kresovich et al. 2015
	↑	0	0	–	–	–	0	Meeker et al. 2010
	↑	–	–	↑	0	–	–	Telisman et al. 2007
	↑	–	–	–	–	–	–	Lewis and Meeker 2015
	0	0	0	–	–	–	–	Mendiola e al. 2011
10–30	0	0	0	–	–	–	–	Hsieh et al. 2009a
	0	0	0	–		–	–	Alexander et al. 1998

Table 2-35. Effects on Reproductive Hormones Associated with Chronic Exposure to Lead (Pb) in Males

PbB (µg/dL)	Hormone							Reference
	T	FSH	LH	E	P	A	SHBG	
30–50	↓	0	0	–	0	–	–	Braunstein et al. 1978
	0	0	0	–	0	–	–	Erfurth et al. 2001
	0	↓	↓	–	–	–	–	Gustafson et al. 1989
	0	↑	↑	–	–	–	–	McGregor and Mason 1990
	↓	↑	↑		0	–	–	Ng et al. 1991
				↑	–	–	–	Telisman et al. 2000
	0	0	0	0	–	–	–	Sadeghnaiit Haghighi et al. 2013
	↓	–	–	–	–	–	–	Rodamilans et al. 1988

0 = no effect; ↑ = increased serum level; ↓ = decreased serum level; – = not evaluated; A = androstenedione; E = estradiol; FSH = follicle stimulating hormone; LH = luteinizing hormone; P = prolactin; SHGB = sex hormone binding globulin; T = testosterone

Effects in Males at Blood Pb Levels ≤10 µg/dL. Cross-sectional studies evaluating adverse effects of non-occupational exposures to Pb on the male reproductive system show that damage to sperm, decreased semen volume, and increased serum testosterone are associated with mean PbB ≤10 µg/dL or with Pb concentrations in semen or spermatozoa when PbBs are ≤10 µg/dL. Results are summarized in Table 2-36, with study details provided in the *Supporting Document for Epidemiological Studies for Lead,* Table 11. None of the studies evaluated associations between PbB and male fertility parameters (i.e., pregnancy). In general, study populations were small (n=61–240), although two studies using NHANES data were of larger populations (Kresovich et al. 2015; Lewis and Meeker 2015). In addition, for a few studies, participants were selected from infertility clinics and it is unclear how this may have biased study results (Meeker et al. 2008, 2010; Mendiola et al. 2011). Despite these limitations, taken together, results of non-occupational exposure studies support that adverse effects to the male reproductive system occur at PbB ≤10 µg/L.

Sperm and semen. A significant association between an increase in PbB ≤10 µg/dL and increasing percentages of morphologically abnormal sperm, wide sperm, and round sperm was observed in a population of Croatian men (Telisman et al. 2007). The mean PbB was 4.92 µg/dL; although the maximum PbB value in this study was 14.9 µg/dL, over 90% of participants had PbB <10 µg/dL. Li et al. (2015) found small, but significant negative associations between PbB and sperm count, sperm concentration, motile sperm, and morphologically normal sperm in 154 men from a reproductive clinic in

Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Effects on serum hormone levels			
Kresovich et al. 2015 Cross-sectional study; n=869	Median:2.0 Quartiles: • Q1: ≤1.4 (reference) • Q2: 1.4–2.1 • Q3: 2.10–3.20 • Q4: >3.20	Testosterone	• **β coefficient ng/mL per µg/dL (SE)** • **Q3: 0.54 (0.21); p<0.05*** • **Q4: 0.79 (0.22); p<0.05*; p-trend=0.00268***
Lewis and Meeker 2015 Cross-sectional study; n=484	Gmean:1.06 Quartiles: • Q1: <0.71 • Q2: 0.71–1.00 • Q3: 1.00–1.59 • Q4: 1.59–33.67	Testosterone	• Percent change in serum testosterone concentration associated with a doubling (100% increase) in PbB: **6.65% (2.09, 11.41); p<0.004)*; p-trend across quartiles=0.003***
Meeker et al. 2010 Cross-sectional study; n=219	Median:1.5 Quartiles • Q1: 1.1 (reference) • Q2: 1.1–1.5 • Q3: 1.5–2.0 • Q4: 2.0–16.2	Testosterone	**Regression coefficient Q4 (ng/dL per µg/dL): 39.9 (3.32, 76.4)***
		FSH	Regression coefficient Q4 (mIU/mL per µg/dL): 0.07 (-0.18, 0.31)
		LH	Regression coefficient Q4 (mIU/m per µg/dL): 0.08 (-0.14, 0.29)
		Inhibin B	Regression coefficient Q4 (pg/mL per µg/dL): -7.79 (-29.0, 13.4)
		SHBG	Regression coefficient Q4 (nmol/L per µg/dL): 0.07 (-0.10, 0.23)
		FAI	Regression coefficient Q4 (per µg/dL): 0.08 (-0.05, 0.21)

Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Mendiola et al. 2011 Case-control study; n=61	Gmean: 2.8	Testosterone	β coefficient (ng/mL per µg/L): -0.12 (-0.40, 0.14)
		FSH	β coefficient (IU/L per µg/L): -0.20 (-0.64, 0.25)
		LH	β coefficient (IU/L per µg/L): -0.07 (-0.49, 0.31)
Telisman et al. 2007 Cross-sectional study; n=240	Median: 4.92	Testosterone	**β coefficient (nmol/L per µg/L): 0.21; p<0.003***
		Estradiol	**β coefficient (nmol/L per µg/L): 0.22; p<0.0008***
		Prolactin	β coefficient (µg per µg/L): -0.18; p<0.007
Sperm and semen quality			
Herandez-Ochoa et al. 2005 Cross-sectional study; n=68	Mean: 9.3 SPZ Pb: 0.047 ng/10^6 cells SF Pb: 2.02 µg/L	Log sperm concentration	**β coefficient SPZ Pb (10^6 cells/mL per ng/10^6 cells): -17.17 (p<0.05)***
		Sperm motility	β coefficient PbB (% per µg/dL): -0.006 **β coefficient SPZ Pb: (% per ng/10^6 cells): -2.12 (p<0.05)***
		Sperm morphology (abnormal)	β coefficient PbB (% per µg/dL): -0.001 **β coefficient SPZ Pb (% per ng/10^6 cells): -1.42 (p<0.05)***
		Sperm viability	β coefficient PbB (% per µg/dL): -0.095 **β coefficient SPZ Pb (% per ng/10^6 cells): -0.130 (p<0.05)***
		Semen volume	β coefficient PbB (mL per µg/dL): -0.043 **β coefficient SF Pb (mL per µg/L): -0.183 mL; p<0.05***

Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Li et al. 2015 Cross-sectional study; n=154	Mean: All participants: 2.78 Low-quality semen group: 3.43 High-quality semen group: 2.38	Low quality sperm	**OR: 1.040 (1.011, 1.069); p=0.0061***
		Decreased sperm concentration	**OR: 1.046 (1.015, 1.078); p=0.0032***
		Decreased sperm number	**OR: 1.041 (1.012, 1.071); p=0.0048***
		Decreased motile sperm	**OR: 1.057 (1.026, 1.089; p=0.0003***
		Decreased morphologically normal sperm	**OR: 1.071 (1.025, 1.118; p=0.0021***
Meeker et al. 2008 Cross-sectional study; n=219	Median:1.50 • Quartiles (Q): ○ Q1: <1.10 ○ Q2: 1.10–1.50 ○ Q3: 1.50–2.00 ○ Q4: 2.00–16.2	Sperm concentration	Regression coefficient (10^6/mL per µg/dL) Q4: 0.02 (-0.39, 0.43)
		Sperm motility	Regression coefficient (% per µg/dL) Q4: 1.10 (-4.56, 6.75)
		Sperm morphology	Regression coefficient (% per µg/dL) Q4: -0.16 (-1.58, 1.26)
		Semen volume	Regression coefficient (mL per µg/dL) Q4: 0.17 (-0.41, 0.74)
Mendiola et al. 2011 Case-control study; n=61	Gmean: 2.8 Median: 2.9	Sperm concentration	β coefficient (10^6/mL per µg/L): 0.08 (-4.1, 5.2)
		Immobile sperm	β coefficient (% per µg/L): -0.49 (-1.8, 0.62)
		morphologically normal sperm	β coefficient(% per µg/L): -0.8 (-3.5, 3.4)

Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Telisman et al. 2007	Median: 4.92	Immature sperm	β coefficient (10^6/mL per µg/L): 0.13 (p<0.07)
Cross-sectional study; n=240		Pathologic sperm	**β coefficient (% per µg/L): 0.31 (p<0.0002)***
		Wide sperm	**β coefficient (% per µg/L): 0.32 (p<0.0001)***
		Round sperm	**β coefficient (% per µ: 0.16 (p<0.03)***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 11 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Asterick indicates association with PB; unless otherwise specified, values in parenthesis are 95% CIs.

CI = confidence interval; FAI = free androgen index; FSH = follicle-stimulating hormone; Gmean = geometric mean; Inhibin B = gonadal dimeric polypeptide hormone; LH = luteinizing hormone; OR = odds ratio; Pb = lead; SF = seminal fluid; SE = standard error; SHBG = sex hormone-binding globulin; SPZ = spermatozoa

Taiwan. The median PbB was 2.78 μg/dL (SD 1.85); range and percentiles were not reported. Other studies have shown associations between Pb levels in semen and/or spermatozoa and increased percentages of morphologically abnormal sperm and decreased sperm motility and viability, although no associations were observed between PbB and these outcomes (Hernandez-Ochoa et al. 2005; Mendiola et al. 2011); mean PbB levels were 9.3 μg/dL in the Hernandez-Ochoa et al. (2005) study and 2.8 μg/dL in the Mendiola et al. (2011) study. No associations were observed between PbB and sperm concentration, motility, or morphologic abnormalities in men at a median PbB of 1.5 μg/dL (Meeker et al. 2008). Semen volume (mL) was negatively associated with PbB at a mean PbB of 9.3 μg/dL; however, 48% of participants had PbB >10 μg/dL (Herandez-Ochoa et al. 2005).

Serum testosterone levels. Significant associations have also been observed between PbB ≤10 μg/dL and increased serum testosterone levels (Table 2-34). Studies using NHANES data found significant positive associations between PbB and serum testosterone levels (Kresovich et al. 2015; Lewis and Meeker 2015). Examined by PbB quartiles, Kresovich et al. (2015) observed significant positive associations between PbB and serum testosterone (ng/L) for PbBs of 2.10–3.20 and >3.2 μg/dL; the median PbB of the study population was 2.0 μg/dL. A doubling of PbB was positively associated with a 6.65% change in serum testosterone; the mean PbB of the study population was 1.06 μg/dL (Lewis and Meeker 2015). The toxicological significance of the observed associations between PbB and serum testosterone has not been established.

Characterization of Effects in Females. As noted above, most epidemiological studies evaluated effects at PbB ≤10 μg/dL, with few studies of PbB >10 μg/dL. Studies of PbB ≤10 μg/dL are discussed in detail in the section below. General trends for studies showing a relationship between PbB ≤10–50 μg/dL and female reproductive effects are shown in Table 2-37. Effects associated with PbB include increased serum levels of estradiol, FSH, and LH at PbB ≤10 μg/dL (Chang et al. 2006; Krieg et al. 2007), decreased fertility at PbB ≤10 μg/dL (Chang et al. 2006), increased time to pregnancy at PbB >30–40 μg/dL (Sallmén et al. 1995), increased spontaneous abortion at PbB ≤10–30 μg/dL (Borja-Aburto et al. 1999; Yin et al. 2008), decreased number of gestational days at PbB >10–40 μg/dL (Jelliffe-Pawlowski et al. 2006), and increased preterm birth at PbB ≤10–50 μg/dL (McMichael et al. 1986; Jelliffe-Pawlowski et al. 2006; Rabito et al. 2014). Although epidemiological studies demonstrate effects on reproductive function, results are inconsistent, with several studies reporting no association between PbB and female reproductive effects (Baghurst et al. 1987; Bloom et al. 2010, 2011, 2015; Garcia-Esquinas et al. 2014; Jackson et al. 2007; Murphy et al. 1990; Perkins et al. 2014; Pollack et al. 2011; Sallmén et al. 1995;

Taylor et al. 2015; Vigeh et al. 2010). Dose-dependence has not been firmly established within the relatively narrow range of PbB (≤10 µg/dL) in most studies.

Table 2-37. Overview of Effects on the Female Reproductive System and Pregnancy Outcomes Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Increased serum hormones (estradiol, FSH, LH)	Chang et al. 2006; Krieg et al. 2007
	Decreased fertility	Chang et al. 2006
	Increased spontaneous abortion	Yin et al. 2008
	Increased preterm birth	Rabito et al. 2014
	Decreased age at menopause	Eum et al. 2014; Popovic et al. 2005
>10–30	Increased spontaneous abortion	Borja-Aburto et al. 1999
	Decreased number of gestational days	Jelliffe-Pawlowski et al. 2006
	Increased preterm birth	McMichael et al. 1986
>30–40	Increased time to pregnancy	Sallmén et al. 1995
	Decreased number of gestational days	Jelliffe-Pawlowski et al. 2006
	Increased preterm birth	Jelliffe-Pawlowski et al. 2006
>40–50	Increased preterm birth	Jelliffe-Pawlowski et al. 2006

FSH = follicle-stimulating hormone; LH = luteinizing hormone

Effects in Females at Blood Pb Levels ≤10 µg/dL. As discussed above, most epidemiology studies evaluating adverse effects of Pb on female reproductive function reported mean PbB ≤10 µg/dL. Although some studies provide evidence showing associations between PbB ≤10 µg/dL and effects on serum reproductive hormones (Chang et al. 2006; Krieg 2007), fertility (Chang et al. 2006), spontaneous abortion (Lamadrid-Figueroa et al. 2007; Yin et al. 2008), and preterm birth (Rabito et al. 2014; Taylor et al. 2015; Vigeh et al. 2011), many studies show no associations between PbB and these outcomes. In general, most studies are limited by small sample sizes, although, as discussed below, some studies were of larger populations. The basis for differences in study outcomes in not readily apparent, although several factors may contribute, including low samples size, timing of evaluations in menstrual and life cycles, and inclusion of study participants identified from fertility clinics. Results are summarized in Table 2-38, with study details provided in the *Supporting Document for Epidemiological Studies for Lead* Table 12.

Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Effects on serum hormone levels			
Chang et al. 2006 Case control study; n=147	Mean: 3.55	Estradiol	**β coefficient pg/mL per µg/dL (SE): 1.18 (0.60); p=0.049***
Jackson et al. 2011 Longitudinal cohort study; n=252	Mean: 0.87	FSH	β coefficient (IU/L per µg/dL): -2.5 (-11.2, 7.0)
		LH	β coefficient (mg/L per µg/dL): 2.5 (-12.3, 19.9)
		Estradiol	β coefficient (pg/mL per µg/dL): 4.9 (-5.0, 15.9)
		Progesterone	β coefficient (ng/mL per µg/dL): 4.6 (-12.2, 24.6)
Krieg 2007 Cross-sectional study; n=3,375	Gmean: 2.2	FSH	• **Slope pre-menopausal (IU/L per µg/dL): 8.3 (2.2); 95% CI 3.8, 12.7; p=0.0006*** • **Slope post-menopausal (IU/L per µg/dL): 22.2 (4.3); 95% CI 13.5, 30.8; p=0.0000*** • **Slope both ovaries removed (IU/L per µg/dL): 32.6 (11.2); 95% CI 10.1, 55.1; p=0.0054***
		LH	• Slope pre-menopausal (IU/L per µg/dL): 1.7 (1.2); 95% CI -0.6, 4.1; p=0.1486 • **Slope post-menopausal (IU/L per µg/dL): 6.2 (1.6); 95% C: 3.0, 9.5; p=0.0003*** • **Slope both ovaries removed (IU/L per µg/dL): 10.0 (4.4); 95% CI 1.1, 18.9; p=0.0279***

Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Pollack et al. 2011 Longitudinal cohort study; n=252	Mean: 0.93	Estradiol	β coefficient (pg/mL per µg/dL): 0.03 (-0.05, 0.11)
		FSH	β coefficient (mIU/mL per µg/dL): -0.01 (-0.07, 0.06)
		LH	β coefficient (ng/mL per µg/dL): 0.02 (-0.06, 0.10)
		Progesterone	β coefficient (ng/mL per µg/dL): 0.06 (-0.04, 0.17)
Fertility			
Bloom et al. 2010 Longitudinal cohort study; n=15	Mean: 0.82	Oocyte fertilization (*in vitro*)	RR: 1.09 (0.72, 1.65).
Bloom et al. 2011 Longitudinal cohort study; n=80	Mean: 1.54	Achieving pregnancy over 12 menstrual cycles	β coefficient (probability of pregnancy per µg/dL): -0.031 (95% CI -1.066, 1.004); p=0.954
Chang et al. 2006 Case control study of 147	Mean: • All: 3.12 • Controls: 2.78 • Cases: 3.55	Infertility	**OR for PbB >2.5 versus ≤2.5 µg/dL: 2.94 (95% CI 1.18, 7.34); p=0.021***
Pregnancy outcome			
Bloom et al. 2015 Case control study of 235	Mean: 0.71 Tertiles (mean): • T1: not reported • T2: 0.55 • T3: 0.73	Duration of gestation	Regression coefficient gestational age per µg/dL) T3: 0.14 (-0.81, 1.09)

Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Garcia-Esquinas et al. 2014 Birth cohort study; n=100	Gmean: 1.83	Duration of gestation	Mean difference in gestational age (weeks) per 2-fold increase in PbB: 0.02 (95% CI -0.44, 0.47)
Gundacker et al. 2010 Cross-sectional study; n=30	Median PbB: 2.5 Median PbPl: 25.8	Spontaneous abortion	**PbPl in women with a history of miscarriage was higher (n=8; p=0.039) than in women with no history of miscarriage (n=22)***
Lamadrid-Figueroa et al. 2007 Cross-sectional study; n=207	Mean PbB: 6.24 (4.48) Mean plasma Pb: 0.014 Mean plasma/blood Pb ratio: 0.22% (tertile values not reported)	Spontaneous abortion	IRR PbB: 0.93; p=0.56 IRR Plasma Pb: 1.12; p=0.22 **Plasma/blood Pb ratio: 1.18; p=0.02*** IRR for T2 plasma/blood Pb ratio: 1.161; p=0.612 **IRR for T3 plasma/blood Pb ratio: 1.903; p=0.015***
Perkins et al. 2014 Birth cohort; n=949	Estimated mean PbB: 0.4 Mean RBC: 1.22 µg/dL Quartile RBC (µg/dL): • Q1: 0.65 • Q2: 0.96 • Q3: 1.27 • Q4: 2.02	Duration of gestation	β coefficient Q4 gestational age (weeks) per µg/dL: -0.17 (-0.51, 0.16)
Rabito et al. 2014 Birth cohort; n=98	Second trimester mean: 0.42 Third trimester mean: 0.45	Preterm birth	**OR second trimester: 1.66 (1.23, 2.23); p<0.01*** **OR third trimester: 1.24 (1.01, 1.52); p=0.04***
Taylor et al. 2013, 2015 Longitudinal cohort study; n=3,870	Mean: 3.67 Median: 3.42	Preterm birth	**OR for PbB ≥5.0: 2.0 (1.35, 3.00); p=0.001***

Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Vigeh et al. 2010 Longitudinal cohort study; n=351	Mean: 3.8	Spontaneous abortion	OR (log PbB): 0.331 (0.011, 10.096); p=0.53
Vigeh et al. 2011 Longitudinal cohort study; n=44 women with preterm birth; n=304 women with term birth	Mean: • Term birth: 3.72 • Preterm birth: 4.52	Preterm birth	**OR: 1.41 (1.08, 1.84)***
Yin et al. 2008 Case-control study; n=80	Control (term birth): 4.5 Spontaneous abortion: 5.3	Spontaneous abortion	**PbB was higher in cases of anembryonic pregnancy during gestational weeks 8–13 compared to controls with term births (p=0.03).***
Zhu et al. 2010 Retrospective cohort; n=43,288 mother-infant pairs (n=3,519 preterm birth; n=39,769 term birth)	**PbB** Mean: 2.1 Quartiles: • Q1: ≤1.0 • Q2: 1.1–2.0 • Q3: 2.1–3.0 • Q4: 3.1–9.9	Preterm birth	Adjusted ORs did not show an increased risk of preterm birth for any quartile. Q4: 1.04 (0.89, 1.22)

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 12 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Asterick indicates association with PB; unless otherwise specified, values in parenthesis are 95% CIs.

CI = confidence interval; FSH = follicle-stimulating hormone; Gmean = geometric mean; IRR = incidence rate ratio; LH = luteinizing hormone; OR = odds ratio; Pb = lead; PbPl = Pb concentration in placenta (µg/kg); RBC = red blood cell; RR = relative risk; SE = standard error

Serum hormone levels and estrus cycle. Results of epidemiological studies on associations between PbB ≤10 μg/dL and serum hormone levels show conflicting results (Table 2-38). The strongest evidence showing that chronic Pb exposure alters serum hormone levels is from a large cross-sectional study (mean PbB 2.2 μg/dL) participating in the NHANES III study (Krieg 2007). Serum levels of FSH (IU/L) increased with PbB in both pre-menopausal and post-menopausal women. Serum levels of LH increased with PbB in post-menopausal women, but not pre-menopausal women. The lowest PbBs associated with a significant increase in FSH in pre- and post-menopausal women were 4.1 μg/dL and 2.4 μg/dL, respectively. The lowest PbB associated with a significant increase in FSH in post-menopausal women was 2.8 μg/dL (slope±SE 8.6±3.3; 95% CI 2.1, 15.2; p=0.0109). Increases in serum FSH and LH were also observed in women who had total ovariectomy, indicating that increased hormone levels may be related to effects on the hypothalamus or pituitary (Krieg 2007). No associations were observed between Pb and serum levels of FSH, LH, estradiol, or progesterone or menstrual cycle length in a smaller study of pre-menopausal women with a mean PbB of 0.87 μg/dL (Jackson et al. 2011). In this same study population, when PbB was examined by tertiles, increased serum progesterone levels were observed in the second PbB tertile (0.73–1.10 μg/dL) compared to the lowest tertile (0.30–0.72 μg/dL), but no effects were observed in the highest PbB tertile (1.11–6.20 μg/dL) compared to the lowest (Pollack et al. 2011). In this study population, no association was observed between PbB and anovulation. In a case-control study of women attending a fertility clinic, a significant association was observed between PbB and serum estradiol concentrations (Chang et al. 2006).

Fertility. Little epidemiological information is available on the effects of PbB ≤10 μg/dL on female fertility. A prospective cohort study with a mean Pb of 1.5 μg/dL showed no effect on achieving pregnancy over 12 menstrual cycles (Bloom et al. 2011). A case-control study of women from a fertility clinic showed a 2.9-fold risk of infertility for PbB >2.5 μg/dL compared to PbB ≤2.5 μg/dL (Chang et al. 2006). In a study of women undergoing *in vitro* fertilization, no association was observed between PbB and oocyte fertilization; however, only 15 women were included in this study. Available epidemiological studies on the effects of PbB ≤10 μg/dL on fertility are limited due to small numbers of participants and study populations of women undergoing fertility treatment; thus, data are not sufficient to determine if fertility in women is affected at PbB ≤10 μg/dL.

Spontaneous abortion. Few epidemiological studies have evaluated associations between PbB ≤10 μg/dL and spontaneous abortion (Table 2-38). Although studies provide some evidence suggesting associations between PbB ≤10 μg/dL or plasma/blood Pb ratio and spontaneous abortion, results are inconsistent. In a case-control study, PbB was significantly higher in cases of spontaneous abortion (PbB 5.3 μg/dL;

p=0.03) during weeks 8–13, compared to women with term birth (PbB 4.5 μg/dL) (Yin et al. 2008). A cross-sectional study reported that the risk of miscarriage per 1 SD increase of plasma/blood Pb ratio [mean plasma/blood Pb ratio±SD (%): 0.22±0.14] was associated with an 18% greater incidence of spontaneous abortion, although the association between risk of spontaneous abortion and PbB (mean 6.24) was not significant (Lamadrid-Figueroa et al. 2007). In contrast, results of a longitudinal cohort study showed no association between PbB and spontaneous abortion during gestational weeks 13–19 (Vigeh et al. 2010).

Preterm birth. Several studies have evaluated associations between PbB ≤10 μg/dL and preterm birth (<37 weeks of gestation), including two studies of larger study populations (n=705–3,870) (Perkins et al. 2014; Taylor et al. 2015). Results of these studies are mixed (Table 2-38). The strongest evidence showing that chronic Pb exposure is associated with preterm birth is from a large, longitudinal cohort study (Taylor et al. 2013, 2015). When stratified into groups of PbB <5 and ≥5.0 μg/dL, there was a 2-fold increase in the risk of preterm birth for PbB ≥5.0 μg/dL compared to PbB <5 μg/dL. In the PbB ≥5.0 μg/dL group, the maximum PbB was 19.14 μg/dL, although very few PbBs were >10 μg/dL; however, the group mean PbB was not reported. The risk of preterm birth also was increased in a longitudinal cohort study (Vigeh et al. 2011). Mean PbB in women with preterm birth was significantly higher than in women with term birth (preterm PbB: 4.52 μg/dL; term birth PbB: 3.72 μg/dL). A cohort study showed increased odds of preterm birth associated with PbB measured in the 2nd (mean: 0.42 μg/dL) and 3rd (mean: 0.45 μg/dL) trimesters (Rabito et al. 2014). ORs for risks of preterm birth were 1.66 (p<0.01) and 1.24 (p=0.04) for 2nd and 3rd trimester PbB, respectively. Other studies reported no associations between PbB and preterm birth at mean PbB of 0.71–1.22 μg/dL (Bloom et al. 2015; Perkins et al. 2014; Zhu et al. 2010), including a large retrospective cohort study (Zhu et al. 2010) and a large case-control study (Perkins et al. 2014).

Age at menopause. A few studies had evaluated associations between Pb exposure and age at menopause (Eum et al. 2014; Popovic et al. 2005). Eum et al. (2014) found a negative association between tibia Pb and age at onset of natural menopause (e.g., non-surgical) in a population of 434 participants in the Nurses Health Study cohort. In the highest tibia Pb tertile, the age at onset of menopause was 1.21 years earlier than controls. However, no associations were observed between PbB (mean PbB: <5 μg/dL) or patella Pb. In a study of 108 former smelters (mean PbB: 2.73 μg/dL), the age at onset of combined natural and surgical menopause was lower by 7 years (p=0.001) compared to controls (n=99; PbB: 1.25 μg/dL) (Popovic et al. 2005). No difference was observed between the age at onset and natural menopause between the exposed and control groups.

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of toxicity to male and female reproductive systems. Oxidative stress through ROS is a plausible mechanism for reproductive effects, as is the disruption of calcium homeostasis. Mechanisms for alterations in circulating hormone levels have been not been established. However, EPA (2014c) and NRC (2012) noted several possible mechanisms that may be involved in alterations of serum hormones, including direct inhibition of LH secretion; reduced expression of steroidogenic acute regulatory protein (a protein required in maintaining gonadotropin-stimulated steroidogenesis); altered release of pituitary hormones due to interference with cation-dependent second messenger systems; and altered binding of hormones to receptors. Pb is distributed to, and has been measured in, semen, spermatozoa, the fetus, umbilical cord blood, placenta, and follicular fluid (see Section 3.1.2, Toxicokinetics, Distribution), providing a toxicokinetic mechanism for direct effects to reproductive tissues.

2.18 DEVELOPMENTAL

This section discusses developmental effects of Pb other than neurodevelopmental defects. Neurodevelopmental effects are discussed in Section 2.16 (Neurological Effects). The term "developmental" used in the discussion that follows refers to effects other than neurodevelopmental.

Overview. Numerous epidemiological studies have evaluated developmental effects (birth outcomes, birth defect, neural tube defects, decreased anthropometric measures in children, and delayed puberty) associated with Pb exposure, with the database for developmental effects dominated by environmental exposure studies with PbB ≤10 μg/dL. In general, studies provide mixed evidence for effects on birth outcomes (e.g., infant size) and anthropometric measures in children, but more consistent evidence for delayed puberty. Although studies provide evidence of associations between PbB and developmental outcomes, results are inconsistent, and several studies, including prospective studies, with PbB ≤10 μg/dL show no associations with developmental outcomes.

The following developmental effects have been associated with PbB:

- ≤10 μg/dL:
    - Effects on birth outcomes (decreased birth weight, head circumference, and crown-heel length); results are mixed when compared across studies.

  - Decreased anthropometric measures in children (weight, height, head circumference, trunk length, leg length, arm length, BMI); results are mixed when compared across studies.
  - Delayed puberty in females (breast development, pubic hair development, onset of menarche); corroborated in multiple studies.
  - Delayed puberty in males (testicular volume, genitalia development, pubic hair development); a few studies with equivocal results.
- >10 μg/dL (based on few studies):
  - Effects on birth outcomes (low birth weight).
  - Decreased anthropometric measures in children (decreased weight, height, head circumference, chest circumference).
  - Delayed puberty in females (breast development).
  - Delayed puberty in males (decreased testicular size, delayed pubic hair development, delayed penile development).

Measures of Exposure. Most studies evaluating developmental effects used maternal PbB and/or cord, infant, or child PbB as the biomarker for exposure. In some studies, Pb concentrations in red blood cells (Perkins et al. 2014), maternal bone (Afeiche et al. 2011; Cantonwine et al. 2010b; Hernandez-Avila et al. 2002; Kordas et al. 2009), or hair (Sanín et al. 2001; Sanna and Vallascas 2011) were used as biomarkers.

Confounding Factors. Numerous complicating factors may add uncertainty in the interpretation of studies examining associations between PbB and developmental effects. Confounding factors include nutrition during pregnancy, prenatal care, adequate nutrition during infancy and childhood, SES, intercurrent diseases, alcohol consumption, smoking status, and potential exposure to other chemicals. Failure to account for possible confounders may overestimate associations between PbB and effects.

Characterization of Effects. As noted above, most epidemiological studies evaluated developmental effects at PbB ≤10 μg/dL, with few studies of PbB >10 μg/dL. Studies of PbB ≤10 μg/dL are discussed in detail in the section below. General trends for studies showing a relationship between PbB ≤10–50 μg/dL and developmental effects are shown in Table 2-39. Effects on birth outcomes, including decreased birth weight, head circumference, and crown-heel length have been observed at maternal PbBs of ≤10–50 μg/dL. Decreased anthropometric measures in infants and children, including decreased weight, height, head circumference, trunk length, leg length, arm length, and BMI, have been observed over the PbB range of ≤10–30 μg/dL. Delayed onset of puberty in males and females was observed over

the PbB range of ≤10–30 µg/dL. Very little data are available regarding *in utero* exposure to Pb and birth defects. Two studies that examined neural tube defects did not find associations with Pb exposure at mean blood levels over for PbB means ranging from 2.4 to 24 µg/dL (Brender et al. 2006; Zeyrek et al. 2009). As discussed below, although epidemiological studies demonstrate developmental effects of Pb, results across studies are inconsistent, with several studies reporting no association between PbB and developmental effects. For example, results of effects on birth outcomes in study populations with maternal PbB ≤10 µg/dL are equivocal (see Tables Table 2-40 and Table 2-41). For studies with maternal PbB >10 µg/dL, equivocal results also were observed for associations between PbB and birth weight and length (Factor-Litvak et al. 1991; Hernandez-Avila et al. 2002; McMichael et al. 1986; Murphy et al. 1990). Dose-dependence has not been firmly established within the relatively narrow range of PbB (≤10 µg/dL) in most studies.

Table 2-39. Overview of Developmental Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Effects on birth outcome (decreased birth weight, crown-heel length, head circumference)	Bornschein et al. 1989; Gonzales-Cossio et al. 1997; Nishioka et al. 2014; Odland et al. 1999; Taylor et al. 2013, 2015; Xie et al. 2013; Zhu et al. 2010
	Minor congenital anomalies	Needleman et al. 1984
	Decreased anthropometric measures in children (decreased weight, height, head circumference, trunk length, leg length, arm length, body mass index)	Afeiche et al. 2011; Dallaire et al. 2014; Hauser et al. 2008; Hong et al. 2014; Ignasiak et al. 2006; Little et al. 2009; Min et al. 2008b; Olivero-Verbel et al. 2007; Schell et al. 2009; Yang et al. 2013a
	Delayed puberty in females (breast development, pubic hair development, onset of menarche)	Denham et al. 2005; Den Hond et al. 2011; Gollenberg et al. 2010; Naicker et al. 2010; Selevan et al. 2003; Wu et al. 2003b
	Delayed puberty in males (testicular volume, genitalia development, pubic hair development)	Hauser et al. 2008; Williams et al. 2010

Table 2-39. Overview of Developmental Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
>10–30	Effects on birth outcome (decreased birth weight)	Chen et al. 2006; Hernandez-Avila et al. 2002
	Decreased anthropometric measures in children (decreased weight, height, head circumference, chest circumference)	Frisancho and Ryan 1991; Tomoum et al. 2010
	Delayed puberty in females (breast development)	Tomoum et al. 2010
	Delayed puberty in males (decreased testicular size, delayed pubic hair development; delayed penile development)	Tomoum et al. 2010
>30–50	Effects on birth outcome (low birth weight)	Jelliffe-Pawlowski et al. 2006

Table 2-40. Effects on Birth Outcomes at Blood Lead Concentration (PbB) ≤10 µg/dL

	Birth outcome			
Reference	Weight	Height or C-H length	SGA	Head circumference
Al-Saleh et al. 2014	0	0	0	0
Bloom et al. 2015	0	0	–	0
Bornschein et al. 1989	↓	↓	–	0
Garcia-Esquinas et al. 2014	0	0	–	–
Gonzalez-Cossio et al. 1997	0	–	–	–
Nishioka et al. 2014	↓	–	–	–
Odland et al. 1999	↓	–	–	–
Perkins et al. 2014	0	0	–	0
Rabito et al. 2014	0	–	–	–
Taylor et al. 2015	↓	↓	–	↓
Thomas et al. 2015	–	–	0	–
Xie et al. 2013	↓	0	–	0
Zhu et al. 2010	↓	–	0	–

↓ = decrease in outcome measure; 0 = no effect on outcome measure; – = not assessed; C-H = crown-heel; SGA = small for gestational age

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Al-Saleh et al. 2014 Cross-sectional study; n=1578 mother-infant pairs	Maternal PbB mean: 2.897	Birth weight	OR: 1.107 (0.797, 1.538); p=0.545
		Birth height	OR: 1.299 (0.945, 1.786); p=0.107
		Crown-heel length	OR: 1.061 (0.795, 1.415); p=0.689
		SGA	OR: 1.168 (0.837, 1.631); p=0.362
		Head circumference	OR: 1.007 (0.724,1.400); p=0.968
		Apgar	OR: 1.027 (0.787, 1.341); p=0.842
Bloom et al. 2015 Case-control study; n=235 mother-infant pairs	Maternal PbB mean: 0.71 Tertiles: • T1: <0.55 (reference) • T2: 0.55-<0.73 • T3: 0.73–2.23	Birth weight	Linear regression coefficient (g per µg/dL) T3: -34.85 (-97.76, 128.06); p-trend=0.202
		Birth length	Linear regression coefficient (cm per µg/dL) T3: 0.14 (-0.81, 1.09); p-trend:0.671
		Head circumference	Linear regression coefficient (cm per µg/dL) T3: -0.33 (-1.07, 0.41); p-trend: 0.132
Bornschein et al. 1989 Prospective study; n=202 mother-infant pairs	**PbB:** Mean (SD): 7.5	Birth weight	**Regression coefficient (g per ln µg/dL) for all births: -114; p<0.001*.** **Regression coefficient (g per ln µg/dL) with significant interaction with maternal age (p=0.0073)*:** **maternal age 18 years: -58*** **maternal age 30 years: -601***
		Birth length	**Regression coefficient (cm per ln µg/dL): -2.5; p=0.019***
		Head circumference	Regression coefficient (cm per ln PbB µg/dL): 0.0 p=0.97

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Garcia-Esquinas et al. 2014 Birth cohort study; n=100 mother-infant pairs	Maternal PbB Gmean: 1.83	Birth weight	Adjusted mean difference in grams for a 2-fold increase in PbB (µg/L): 62.4 (-73.1, 197.8)
		Birth length	Adjusted mean difference in cm for a 2-fold increase in PbB (µg/L): 0.17 (-0.56, 0.91)
		Abdominal diameter	Adjusted mean difference in cm for a 2-fold increase in PbB (µg/d): 0.31 (-0.52, 1.15)
		Cephalic diameter	Adjusted mean difference in cm for a 2-fold increase in PbB (µg/L): 0.15 (-0.21, 0.51)

Gonzalez-Cossio et al. 1997
 	
Birth cohort study;
n=272 mother-infant pairs
	PbB:
	• Maternal
	  ○ Mean (SD): 8.9 (4.1)
	  ○ Quartiles:
	  ▪ Q1: ≤5.8
	  ▪ Q2: 5.9–8.0
	  ▪ Q3: 8.1–11.0
	  ▪ Q4: ≥11.1
	• Umbilical cord
	  ○ Mean (SD): 7.1 (3.5)
	  ○ Quartiles
	  ▪ Q1: ≤4.6
	  ▪ Q2: 4.7–6.1
	  ▪ Q3: 6.2–8.5
	  ▪ Q4: ≥8.6
		Birth weight	Regression coefficient:
			• Maternal PbB for Q4: -98.30 (59.55); p=0.100
			• Umbilical cord PbB for Q4: -41.74 (64.04); p=0.514

Nishioka et al. 2014 Cohort study; n=386 mother-infant pairs	Maternal PbB mean at gestational weeks: • 12 weeks: 0.98 • 25 weeks: 0.92 • 36 weeks: 0.99	Birth weight	Regression coefficient based on log µg/dL: • **Infant males: -0.151 (p<0.05)*** • Infant females: -0.098 (p>0.05)

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Odland et al. 1999 Cohort study; n=262 mother-infant pairs	Maternal, mean (range); p-values compare Russian and Norwegian cohorts • Russian cohort: 2.9 (0.83–13.5) • Norwegian cohort: 2.3 (0.41–3.9); p<0.001	Birth weight	Regression coefficient, combined Russian and Norwegian cohorts [g per µmol/L (g per 20.7 µg/dL)]: **-1,068 (95% CI -2,134, -2); p<0.05***
Perkins et al. 2014 Birth cohort study; n=829 mother-infant pairs	Maternal RBC Pb concentration (µg/dL) mean: 1.22 Quartiles for RBC Pb; mean: • Q1: 0.65 • Q2: 0.96 • Q3: 1.27 • Q4: 2.02 Estimated maternal PbB mean: 0.4	Birth weight	Linear regression β coefficient for RBC (µg/dL) Q4: -47 (-128, 35); p-trend: 0.27
		Birth length	Linear regression β coefficient for RBC (µg/dL) Q4: -0.15 (-0.54, 0.23); p-trend: 0.37
		Head circumference	Linear regression β coefficient for RBC (µg/dL) Q4: -0.08 (-0.33, 0.16); p-trend: 0.56
Rabito et al. 2014 Birth cohort study; n=98 mother-infant pairs	Maternal 2nd trimester PbB mean: 0.42 Maternal 3rd trimester PbB mean: 0.45	Birth weight	Linear regression β coefficient, g per µg/dL maternal: • 2nd trimester: -43.21 (-88.6, 2.18); p=0.06 • 3rd trimester: β not reported; p=0.68 • Delivery: β not reported; p=0.83

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Taylor et al. 2013, 2015 Longitudinal cohort study; n= 4,285 mother-infant pairs	Maternal PbB mean: 3.67 Population stratified by PbB <5.0 and ≥5.0	Birth weight	**β coefficient (g per µg/dL): -13.23 (-23.75, -2.70); p=0.014***
		Head circumference	**β coefficient (cm per µg/dL): -0.04 (-0.07, -0.06)[e]; p=0.021***
		Crown-heel length	**β coefficient (cm per µg/dL): -0.05 (-0.10, -0.00); p=0.034***
Thomas et al. 2015 Prospective cohort; n=1,835 mother-infant pairs	Maternal PbB median: 0.59 Tertiles: • T1: <0.52 • T2: 0.52–1.04 • T3: >1.04–4.04	SGA	Adjusted RR for T3 (95% CI): 1.19 (0.65, 2.18)
Xie et al. 2013 Birth cohort study; n=252 mother-infant pairs	Maternal PbB mean: 3.53	Birth weight	**β coefficient (g per square root µg/dL): -148.99 (-286.33, -11.66); p=0.03***
		Birth length	β coefficient (cm per square root µg/dL): -0.46 (-1.25, 0.34); p=0.26
		Head circumference	β coefficients (cm per square root µg/dL): -0.37 (-0.78, 0.19); p=0.24

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Zhu et al. 2010 Retrospective cohort study; n=43,288 mother-infant pairs	Maternal PbB mean: 2.1	Birth weight	**β coefficient g per µg/dL (95% CI):** 0: reference **1: -27.4 (-17.1, -37.8)*** **2: -38.8 (-24.1, -53.4)*** **3: -47.5 (-29.6, -65.4)*** **4: -54.8 (-34.2, -75.5)*** **5: -61.3 (-38.2, -84.4)*** **6: -67.2 (-41.8, -92.5)*** **7: -72.5 (-45.2, -99.9)*** **8: -77.6 (-48.3, -106.8)*** **9: -82.3 (-51.2, -113.3)*** **10: -86.7 (-54.0, -119.4)***
		SGA	Adjusted OR for Q4: 1.07 (0.93, 1.23)

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 13 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Values are for maternal PbB, unless otherwise specified.
[d]Asterick indicates association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[e]Values are reported; the value for the β coefficient is outside of the 95% CI.

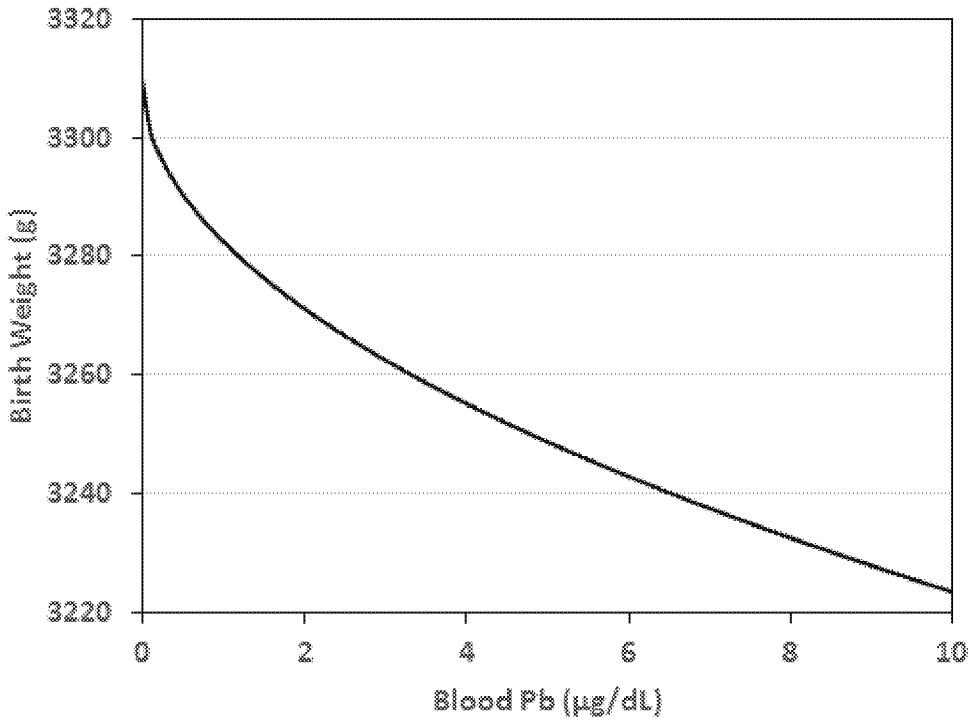
CI = confidence interval; NS = not statistically significant; OR = odds ratio; Pb = lead; RBC = red blood cell; RR = relative risk; SGA = small for gestational age

Effect at Blood Pb Levels ≤10 µg/dL. Epidemiology studies have reported developmental effects, including birth outcomes, birth defects, anthropometric measures in children, and delayed onset of puberty, at mean PbB ≤10 µg/dL. Study details are provided in *Supporting Document for Epidemiological Studies for Lead,* Table 13. Results of studies on associations between PbB and adverse effects on birth outcomes and anthropometric measures are mixed when compared across studies. Delayed onset of puberty in females has been corroborated in several studies. Fewer studies are available regarding effects of Pb on onset of puberty in males, with equivocal results. Exposure to Pb has not been shown to cause birth defects in humans. Neural tube defects have not been associated with Pb exposure and findings of a single study showing minor anomalies have not been corroborated.

Birth outcomes. An overview of results of studies that evaluated associations between Pb exposure and birth outcomes (infant weight, height or crown-heel length, small for gestation age [SGA], and head circumference) at maternal PbB ≤10 µg/dL is shown in Table 2-40, with more detailed results in Table 2-41. Studies include two prospective studies (Bornschein et al. 1989; Thomas et al. 2015), several studies of large populations (n=829–43,288) (Al-Saleh et al. 2014; Perkins et al. 2014; Taylor et al. 2015; Thomas et al. 2015; Zhu et al. 2010), and cohort and case-control studies of smaller (n=98–386) populations (Bloom et al. 2015; Garcia-Esquinas et al. 2014; Gonzalez-Cossio et al. 1997; Nishioka et al. 2014; Rabito et al. 2014). As shown in Table 2-41, results of these studies show either decreases or no change in birth outcomes. In a small (n=202) prospective study, Bornschein et al. (1989) reported associations between maternal PbB (mean 7.5 µg/dL) and decreased birth weight and length. The size of the effect of PbB varied with maternal age ($p<0.007$), with a 58 g per lnPbB decrease for pregnancies at age 18 years and a 601 g decrease per ln PbB (µg/dL) for pregnancies at age 30 years. In the complete birth cohort from this study, which included mothers who declined participation in the infant follow-up (n=861), the decline in birth weight was -114 g per ln PbB. Results of the largest cohort study, a retrospective study of >43,000 participants (mean PbB 2.1 µg/dL), showed a negative association between PbB and birth weight (Zhu et al. 2010). The best fitting model was a linear change in birth weight with square root of PbB (Figure 2-7). The model predicts a 34 g decrease in birth weight for an increase in PbB from 1 to 5 µg/dL and a 59 g decrease for an increase in PbB from 1 to 10 µg/dL (adjusted for confounders). Results of a longitudinal cohort study of 4,285 mother-infant pairs (maternal PbB mean: 2.1 µg/dL; range 0.42–19.14) showed negative associations between birth weight, crown-heel length, and head circumference for participants with PbB ≥5 µg/dL compared to PbB <5 µg/dL (Taylor et al. 2015). Other smaller cohort studies also showed associations between maternal PbB ≤10 µg/dL and decreased birth weight (Nisioka et al. 2014; Odland et al. 1999). In contrast, other studies, including a prospective study and cohort studies of large populations, did not find associations between PbB and birth outcome

measures. A prospective study of 1,835 mother-infant pairs did not find an association between PbB and SGA, with PbB data stratified by tertiles (range for highest tertile: 1.04–4.04 μg/dL) (Thomas et al. 2015). Similarly, no associations between maternal PbB and decreased birth weight, length, or head circumference were observed in a cohort study of 829 participants (estimated PbB mean of 0.4 μg/dL) (Perkins et al. 2014), or in a cross-sectional study of 1,578 participants (Al-Saleh et al. 2014). Smaller cohort studies also report no associations between PbB and adverse birth outcome measures (Bloom et al. 2015; Garcia-Esquinas et al. 2014; Gonzalez-Cossio et al. 1997; Rabito et al. 2014). Equivocal findings for birth outcomes in studies examining effects at maternal PbB ≤10 μg/dL are not surprising, given that prospective studies at maternal PbB >10 μg/dL also have reported conflicting results for adverse effects on birth outcomes (Factor-Litvak et al. 1991; Hernandez-Avila et al. 2002; McMichael et al. 1986; Murphy et al. 1990). For example, two prospective studies found no associations between PbB and birth weight in birth cohorts that had mean maternal PbBs >10 μg/dL (Factor-Litvak et al. 1991; McMichael et al. 1986).

Figure 2-7. Relationship Between Blood Lead Concentration (PbB) and Birth Weight at PbB ≤10 μg/dL



Source: Zhu et al. 2010

Birth defects. Few studies have evaluated associations between *in utero* exposure to Pb and birth defects. Details of studies evaluating PbB ≤10 μg/dL are provided in the *Supporting Document for Epidemiological Studies for Lead,* Table 13. No association was observed between PbB and neural tube defects in a case-control study (n=409) with mean maternal PbB of 2.5 μg/dL (Brender et al. 2006). Other epidemiological studies that have reported associations between Pb in exposure media (e.g., water, soil) and neural tube defects are limited by the lack of PbB measurement (Bound et al. 1997; Huang et al. 2011; Irgens et al. 1998). An early cross-sectional study of birth outcomes examined associations between PbB and congenital anomalies using hospital records on 5,183 deliveries in Boston, Massachusetts (Needleman et al. 1984). The RR of an anomaly increased with increasing cord PbB; the RR (relative to PbB 0.7 μg/dL) was 1.87 (95% CI 1.44, 2.42) for PbB of 6.3 μg/dL and increased to 2.39 (95% CI 1.66, 3.43) at 15 μg/dL and 2.73 (95% CI 1.80, 4.16) at 24 μg/dL. The anomalies were considered to be minor (hemangiomas, lymphangiomas, hydrocele, minor skin anomalies, undescended testicle) and no specific anomaly was associated with PbB. Limitations of this study are that it was a cross-sectional study of a convenience sample with outcomes obtained from hospital records. Associations between PbB and congenital anomalies have not been corroborated.

Anthropometric measures in children. An overview of results of studies evaluating associations between Pb exposure and growth of infants and children (aged 0.5–15 years) at maternal and/or offspring PbB ≤10 μg/dL is shown in Table 2-42, with more detailed results in Table 2-43. Studies include two prospective studies (Dallaire et al. 2014; Lamb et al. 2008), cross-sectional studies of large (n=899–1,050) populations (Afeiche et al. 2011; Hong et al. 2014; Ignakiak et al. 2006), and several smaller (n=108–489) cohort and cross-sectional studies (Hauser et al. 2008; Little et al. 2009; Min et al. 2008b; Olivero-Verbel et al. 2007; Schell et al. 2009; Yang et al. 2013a). Most studies report negative associations between Pb exposure and height, with mixed results for weight and BMI (Table 2-42). A small (n=290) prospective study showed an association between cord PbB (mean 4.8 μg/dL) and small decreases in height and head circumference, but not for weight or BMI (Dellaire et al. 2014). Similarly, Lamb et al. (2008) did not find an association between maternal PbB and height or BMI at maternal PbB means of 5.60–20.56 μg/dL (means for different geographic locations). In contrast, results of large case-control studies showed negative associations between maternal bone Pb and weight (Afeiche et al. 2011), maternal PbB and weight and height (Hong et al. 2014), and child PbB and several growth measures, including weight, height, and BMI (Ignasiak et al. 2006). The largest negative association for decreased weight was observed for maternal bone Pb in females assessed at 2–5 years of age; the mean PbB in children was 3.8 μg/dL (Afeiche et al. 2011). At the 5-year assessment, body weight in females was decreased by approximately 172 g for each 1-SD increase in maternal bone Pb. Smaller case-control and

cohort studies reported consistent negative associations between PbB and height, with equivocal findings for weight, and no associations for BMI.

Table 2-42. Overview of Decreased Anthropometric Measures in Children at Blood Lead Concentration (PbB) ≤10 µg/dL

Reference	Age at time of assessment (years)	Anthropometric measurements		
		Weight	Height	BMI
Afeiche et al. 2011	1–5	↓ (F); 0 (M)	–	–
Dallaire et al. 2014	8–14	0	↓	0
Hauser et al. 2008	8–9	0	↓	0
Hong et al. 2014	0.5–2	↓	↓	–
Ignasiak et al. 2006	7–15	↓ (F); 0 (M)	↓ (F); 0 (M)	↓
Lamb et al. 2008	1–10	0	0	0
Little et al. 2008	2–12	↓	–	–
Min et al. 2008b	5–13	0	↓	–
Olivero-Verbel et al. 2007	5–9	0	↓	–
Schell et al. 2009	0.5–1	0	↓	–
Yang et al. 2013a	3–9	↓	↓	0

↓ = decrease in outcome measure; 0 = no effect on outcome measure; – = not assessed; BMI = body mass index; F = females; M = males

Delayed puberty. Results of studies that evaluated associations between Pb exposure and sexual maturation in boys and girls at child PbB ≤10 µg/dL are summarized in Table 2-44. In girls, delayed onset of puberty, as measured by breast development, pubic hair development, and attainment of menarche, has been corroborated in multiple cross-sectional studies (Den Hond et al. 2011; Denham et al. 2005; Gollenberg et al. 2010; Naicker et al. 2010; Selevan et al. 2003; Wu et al. 2003b). Mean PbB in these studies ranged from 0.49 to 4.9 µg/dL. Delays in the predicted attainment of menarche ranged from 3.6 to 10.6 months (Denham et al. 2005; Selevan et al. 2003). Fewer studies examining associations between Pb exposure and sexual maturation in boys at child PbB ≤10 µg/dL are available. Results of these studies are equivocal. Delayed sexual maturation, measured by genitalia development, testicular volume, and pubic hair development, was observed in two cross-sectional studies of the same study population of 489 boys; the median child PbB was 3 µg/dL (Hauser et al. 2008; Williams et al. 2010). However, no association between PbB and the onset of puberty was observed in a cross-sectional study of 887 boys with a median PbB of 2.5 µg/dL (Den Hond et al. 2011).

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Afeiche et al. 2011 Cross-sectional study; n=999 mother-child pairs	• Child PbB mean: 3.8 • Maternal bone Pb (patella) mean (µg/g): 10.4	Weight (females)	Associations between a 1-SD increase in maternal bone Pb (µg/g) and child weight (g) for children aged: • 12 months: -70.9 (-147.9, 6.0) • **24 months: -96.1 (-170.4, -21.8)*** • **36 months: -121.3 (-200.0, -42.6)*** • **48 months: -146.4 (-235.5, -57.4)*** • **60 months: -171.6 (-275.2, -68.0)***
		Weight (males)	Associations between a 1-SD increase in maternal bone Pb (µg/g) and child weight (g) for children aged: • 12 months: 29.4 (-42.1, 100.8) • 24 months: 27.8 (-43.5, 99.1) • 36 months: 7.9 (-67.3, 83.1) • 48 months: -13.6 (-97.9, 70.8) • 60 months: -35.0 (-132.4, 62.3)
Dallaire et al. 2014 Prospective cohort study; n=290 children (aged 8–14 years)	• Cord PbB mean: 4.8 • Child PbB mean: 2.7	Height	**β coefficients (cm per µg/dL cord): -1.57; p=0.004***
		Head circumference	**β coefficients (cm per µg/dL cord): -0.005; p=0.04***
		Weight	β coefficients (kg per µg/dL cord): β not reported; p=0.70
		BMI	β coefficients (kg/m^2 per µg/dL cord): 0.07; p=0.23

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Hauser et al. 2008 Cross-sectional study n=489children (aged 8–9 years)	Child PbB, mean: 3	Height	**Regression coefficient (cm per µg/dL): -1.439 (-2.25, -0.63); p<0.001***
		Weight	Regression coefficient (kg per µg/dL): -0.761 (-1.54, 0.02); p=0.067
		BMI	Regression coefficient (kg/m^2 per µg/dL): -0.107 (-0.44, 0.23); p=0.53
Hong et al. 2014 Cross-sectional study; n=1,150 infants (aged 6–24 months)	Maternal PbB mean: 1.25	Weight	**Weight z score: -0.28 (-0.48, -0.09); p<0.05***
		Height	**Height z score: -0.28 (-0.49, -0.06); p<0.05***
Ignasiak et al. 2006 Cross-section study; n=899 children (aged 7–15 years)	Child PbB mean: 7.7	Weight	• Slope boys(kg per $\log_{10}$ µg/dL): 4.00 (2.45); p=0.10 • **Slope girls (kg per $\log_{10}$ µg/dL): -6.59 (2.09); p=0.001***
		Height	• Slope boys (cm per $\log_{10}$ µg/dL): -6.26 (1.40); p=0.002 • **Slope girls (cm per $\log_{10}$ µg/dL): -5.54 (2.05); p=0.007***
		BMI	• Slope boys (kg/m^2 per $\log_{10}$ µg/dL): -0.39 (0.82); p=NS • **Slope girls (kg/m^2 per log µg/dL): -1.86 (0.75); p=0.01***
		Trunk length	• **Slope(boys (cm per $\log_{10}$ µg/dL): -2.21 (0.97); p=0.02*** • Slope girls (cm per log µg/dL): -1.47 (1.00); p=NS

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
		Leg length	• **Slope boys (cm per log_{10} µg/dL): -4.05 (1.27); p=0.002*** • **Slope girls (cm per log_{10} µg/dL): -4.08 (1.27) p=0.0001***
		Arm length	• **Slope boys (cm per µg/dL): -3.20 (0.97); p=0.0001*** • **Slope girls (cm per log_{10} µg/dL): -2.61 (0.98); p=0.008***
		Trunk-length ratio	• **Slope boys (per log_{10} µg/dL): 0.71 (0.34): p=0.04*** • **Slope girls (per log_{10} µg/dL): 1.03 (0.34); p=0.003***
Lamb et al. 2008 Population-based prospective cohort; n=309 children (aged 1–10) years	Maternal PbB mean for towns of: • Pristina: 5.60 • Mitrovica: 20.56	Height/BMI	Pristina (β coefficients per log µg/dL): • Age 1 year: -0.61 (-2.24, 1.03) • Age 10 years: -0.09 (-3.69, 3.52) Mitrovica (β coefficients per log µg/dL): • Age 1 year: -0.30 (-2.55, 1.96) • Age 10 years: -2.87 (-6.21, 0.47)
Little et al. 2009 Cross-sectional study; n=360 children (aged 2–12 years)	Child PbB mean • 1980 cohort: 23.6 • 2002 cohort: 1.6 • Pooled cohort PbB mean not reported	Height	**β coefficient (cm per10 µg/dL PbB decrease): 2.1 (1.9, 2.3); p<0.0001***
		Weight	**β coefficient (kg per 10 µg/dL PbB decrease): 1.9 (1.7, 2.1); p<0.0001***
		BMI	**β coefficient (kg/m^2 per 10 µg/dL PbB decrease): 0.5 (0.4, 0.7); p<0.0001***

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Min et al. 2008b Cross-sectional study; n=108 children (aged 5–13 years)	Child PbB mean: 2.4	Height	**Regression coefficient cm per µg/dL (SE): -1.449 (0.639); p=0.026***
		Weight	Regression coefficient kg per µg/dL (SE): -0.646 (0.718); 0.370
		BMI	Regression coefficient kg/m^2 per µg/dL (SE): -0.006 (0.272); p=0.982
		Arm length	**Regression coefficient cm per µg/dL (SE): -1.804 (0.702); p=0.012***
Olivero-Verbel et al. 2007 Cross-sectional study; n=189 children (aged 5–9 years)	Child PbB mean: 5.53	Height	**Correlation coefficient: -0.224; p=0.002***
		Weight	Correlation coefficient: -0.126; p=0.087
Schell et al. 2009 Longitudinal cohort study; n=244 children (aged 3–12 months)	Maternal PbB mean: 2.8	Length	Regression coefficients (SE): • **6 months (cm per log µg/dL): 0.149 (0.076); p=0.05*** • 12 months (cm per log µg/dL): 0.073 (0.083); p=0.38
		Weight-for-age	Regression coefficients (SE): • 6 months (kg per µg/dL): 0.013 (0.098); p=0.89 • 12 months (kg per µg/dL): 0.124 (0.107); p=0.25
		Weight for length	Regression coefficients (SE): • 6 months(per µg/dL): -0.158 (0.111); p=0.16 • 12 months (per µg/dL): 0.084 (0.111); p=0.45

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
		Head circumference	Regression coefficients (SE): • **6 months (cm per µg/dL): -0.242 (0.094); p=0.01*** • **12 months (cm per µg/dL): -0.220 (0.109); p=0.05***
		Upper arm circumference	Regression coefficients (SE): • 12 months (cm per µg/dL):-0.132 (0.114); p=0.25
Yang et al. 2013a Cross sectional study; n=246 children (aged 3–8 years)	Child PbB mean: 7.30	Height	**β coefficient(cm per µg/dL): -0.10; p=0.02***
		Weight	**β coefficient (kg per µg/dL): -0.14; p=0.01***
		BMI	β coefficient (kg/m^2 per µg/dL): -0.08;p=0.24

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 13 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Values are for maternal PbB, unless otherwise specified.
[d]Asterick indicates association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.

BMI = body mass index; CI = confidence interval; NS = not statistically significant; OR = odds ratio; Pb = lead; SD = standard deviation; SE = standard error

Table 2-44. Summary of Epidemiological Studies Evaluating the Onset of Puberty at Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Onset of puberty in females			
Den Hond et al. 2011 Cross-sectional study; n=792 girls (aged 14–15 years)	Median: 1.81	Pubic hair development	**OR: 0.65 (0.45, 0.93); p=0.020***
Denham et al. 2005 Cross-sectional study; n=138 girls (aged 10–16.9 years)	Mean: 0.49	Attainment of menarche	**β coefficient (SE) predicting likelihood of attaining menarche (per ln µg/dL): -1.29 (0.494); p=0.01***
Gollenberg et al. 2010 Cross-sectional study; n=705 girls (aged 6–11 years)	Median: 2.5 Tertiles • T1: <1.0 • T2: 1–4.99 • T3: ≥5.00	Inhibin B pubertal cutoff value	**OR for exceeding pubertal cutoff value:** • **T2 (OR): 0.38 (0.12, 1.15)*** • **T3 (OR): 0.26 (0.11, 0.60)***
Naicker et al. 2010 Cross-sectional, longitudinal study; n=682 girls (aged 13 years)	Mean: 4.9	Breast development	**Trend analysis over ages 8–16 years: p<0.001***
		Pubic hair development	**Trend analysis over ages 8–16 years: p<0.001***
		Attainment of menarche	**Trend analysis over ages 8–16 years: p<0.001***

Table 2-44. Summary of Epidemiological Studies Evaluating the Onset of Puberty at Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Selevan et al. 2003 Cross-sectional study; n=2,186 girls (aged 8–18 years)	Gmean • NHW: 1.4 • NHAA: 2.1 • MA: 1.7	Breast development	• NHW OR: 0.82 (0.47, 1.42) • **NHAA OR: 0.64 (0.42, 0.97); p<0.05*** • **MA OR: 0.76 (0.63, 0.91); p<0.05***
		Pubic hair development	• NHW OR: 0.75 (0.37, 1.51) • **NHAA OR: 0.62 (0.41, 0.96); P<0.05** • **MA OR: 0.70 (0.54, 0.91); p<0.05**
		Age of menarche	• NHW HR: 0.74 (0.55, 1.002) • **NHAA HR: 0.78 (0.63, 0.98); p<0.05 (age at menarche delayed 3.6 months)*** • MA HR: 0.90 (0.73, 1.11)
Wolff et al. 2008 Cross-sectional study; n=192 girls (aged 9 years)	Median: 2.4	Breast development	PR for breast stage ≥2 versus stage 1: 1.01 (0.79,1.30)
		Pubic hair development	PR for pubic hair stage ≥2 versus stage 1: 1.25 (0.83, 1.88)
Wu et al. 2003b Cross-sectional study; n=1,706 girls (aged 8–16 years)	Mean: 2.5 Tertiles: • T1: 0.7–2.0 (reference) • T2: 2.1–4.9 • T3: 5.0–21.7	Breast development	• OR for T2: 1.51 (0.90, 2.53) • OR for T3: 1.20 (0.51, 2.85)
		Pubic hair development	• **OR for T2: 0.48 (0.25, 0.92)*** • **OR for T3: 0.27 (0.08, 0.93)***
		Attainment of menarche	• **OR for T2: 0.42 (0.18, 0.97)*** • **OR for T3: 0.19 (0.08, 0.43)***
Onset of puberty in males			
Den Hond et al. 2011 Cross-sectional study; n=887 boys (aged 12–15 years)	Median: 2.50	Onset of puberty	No association between PbB and the onset of puberty (specific data not reported)

Table 2-44. Summary of Epidemiological Studies Evaluating the Onset of Puberty at Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Hauser et al. 2008 Cross-sectional study; n=489 peripubertal boys (aged 8–9 years)	Median: 3	Genitalia development	**OR for having entered genitalia stage G2 for PbB ≥5 compared to PbB <5: 0.57 (0.34, 0.95); p=0.03***
Williams et al. 2010 Longitudinal cohort; n=489 peripubertal boys (aged 8–9 years)	Median: 3	Testicular volume	**HR for testicular volume <3 mL for PbB ≥5 µg/dL compared to PbB <5 µg/dL: 0.73 (0.55, 0.97); p=0.03***
		Genitalia stage	**HR for having entered genitalia stage G2 for PbB ≥5 µg/dL compared to PbB <5 µg/dL: 0.76 (0.59, 0.98); p=0.04***
		Pubic hair stage	HR for having entered pubic hair stage G2 for PbB ≥5 µg/dL compared to PbB <5 µg/dL: 0.69 (0.44, 1.07); p=0.10

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 13 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Values are for maternal PbB, unless otherwise specified.
[d]Asterick indicates association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.

CI = confidence interval; MA = Mexican Americans; NHW = Non-Hispanic whites; NHAA = Non-Hispanic African Americans; NS = not statistically significant; OR = odds ratio; Pb = lead; PR = prevalence ratio; SE = standard error

Associations Between Bone Pb and Birth Outcome and Post-Natal Growth. Studies evaluating associations between maternal bone Pb and birth outcome (birth weight and length, head circumference) and postnatal growth (infant and child weight gain) are summarized in Table 2-45. Studies were conducted in mother-infant/child pairs residing in Mexico City. Maternal tibia Pb was negatively associated with birth weight (Cantonwine et al. 2010b; Gonzalez-Cossio et al. 1997; Kordas et al. 2009), birth length (Hernandez-Avila et al. 2002), and head circumference (Hernandez-Avila et al. 2002; Kordas et al. 2009). Maternal patella Pb was associated with decreased head circumference (Hernandez-Avila et al. 2002), but not birth weight (Afeiche et al. 2011; Gonzalez-Cossio et al. 1997) or birth length (Hernandez-Avila et al. 2002). Infant weight gain measured at 1 month of age was negatively associated with maternal patella Pb, but not maternal tibia Pb (Sanin et al. 2001); no associations between maternal tibia or patella Pb were observed from birth to 12 months of age (Afeiche et al. 2011). Maternal patella Pb was negatively associated with weight gain in girls, but not boys, at 5 years of age; however, no associations were observed for maternal tibia Pb for boys or girls. Taken together, results of these studies provide evidence that long-term maternal Pb exposure is negatively associated with infant size and post-natal growth.

Table 2-45. Associations Between Maternal Bone Pb and Birth Outcome and Postnatal Growth

		Effect				
Reference	Population[a]	Birth weight	Birth length	Head circumference	Infant weight gain	Child weight gain[b]
Afeiche et al. 2011	Mother-infant pairs (522 boys; 477 girls)	0 T (M, F) 0 P (M, F)	–	–	0 T (M, F)[c] 0 P (M, F)[c]	0 T (M, F) 0 P (M) ↓ P (F)
Cantonwine et al. 2010b	538 mother-infant pairs	↓ T	–	–	–	–
Gonzalez-Cossio et al. 1997	272 mother-infant pairs	↓ T 0 P	–	–	–	–
Hernandez-Avila et al. 2002	223 mother-infant pairs	–	↓ T 0 P	↓ T ↓ P	–	–
Kordas et al. 2009	474 mother-infant pairs	↓ T	0 T	↓ T	–	–

Table 2-45. Associations Between Maternal Bone Pb and Birth Outcome and Postnatal Growth

		Effect				
Reference	Population[a]	Birth weight	Birth length	Head circumference	Infant weight gain	Child weight gain[b]
Sanin et al. 2001	329 mother-infant pairs	–	–	–	0 T[d] ↓ P[d]	–

[a]From Mexico City.
[b]Measured at 5 years of age.
[c]Measured from birth to 12 months of age.
[d]Measured at 1 month of age.

↓ = negative association; 0 = no association; – = not reported; F = female; M = male; P = patella; Pb = lead; T = tibia

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in adverse development effects. EPA (2014c) specifically noted that delayed puberty may result from alterations in pulsatile release of sex hormones and that insulin-like growth factor 1 (IGF-1) may play a role in this effect. Pb is distributed to the fetus and has been measured in umbilical cord blood, placenta, and follicular fluid (See Section 3.1.2, Toxicokinetics, Distribution), providing a toxicokinetic mechanism for direct exposure of the fetus.

2.19 CANCER

Overview. Numerous epidemiological studies have investigated associations between Pb exposure and cancer. Studies include exposure of workers and general populations, with many studies reporting PbB. In most studies, mean PbBs in these studies are <10 µg/dL. Although studies provide limited evidence of carcinogenicity of Pb in humans, results are inconsistent and interpretation may be limited due to confounding factors.

Many studies of occupational cohorts and cancer risks do not report PbB data. These studies have reported associations between occupational exposure to Pb and cancer, including overall cancer mortality and cancers of the lung, brain, stomach, kidney, and bladder. However, results are inconsistent and interpretation may be limited due to confounding factors.

The following cancers have been associated with PbB:

- ≤10 μg/dL:
  - Increased risk of all cancer; evaluated in multiple studies with mixed results.
  - Increased risk of lung cancer; evaluated in multiple studies with mixed results.
- >10 μg/dL:
  - Increased risk of all cancer; evaluated in multiple studies with mixed results.
  - Increased risk of respiratory tract cancers (bronchus, trachea, lung); evaluated in multiple studies with mixed results.
  - Increased risk of stomach cancer; evaluated in multiple studies with mixed results.
  - Increased risk of intestinal cancer.
  - Increased risk of cancer of the larynx.
  - Increased risk of glioma.

Carcinogenicity Classifications of Pb and Pb Compounds. IARC has classified inorganic Pb compounds as probably carcinogenic to humans (Group 2A) based on sufficient evidence in animals and limited evidence in humans; evidence for organic Pb compounds was considered to be inadequate in humans and animals (IARC 2006). The National Toxicology Program 14th Report on Carcinogens classified Pb and Pb compounds as reasonably anticipated to be human carcinogens (NTP 2016). As the basis of the Group 2A classification for inorganic Pb compounds, IARC (2006) cited multiple animal studies showing kidney cancer following chronic oral and parenteral exposure (Azar et al. 1973; Balo et al. 1965; Fears et al. 1989; Kasprzak et al. 1985; Koller et al. 1985; Van Esch and Kroes 1969; Zawirska 1981; Zollinger 1953), renal tubular adenoma in offspring of mice exposed during gestation and lactation (Waalkes et al. 1995), and brain gliomas following oral exposure of rats (Zawirska 1981; Zawirska and Medras 1972). For epidemiological studies of occupational cohorts, IARC (2006) noted limited evidence of carcinogenicity of the lung, stomach, kidney, and brain/nervous system, although studies yielded inconsistent results, and interpretation of results was compromised due to potential confounding factors (e.g., smoking, occupational exposure to other carcinogens such as arsenic).

Confounding Factors. Numerous confounding factors can influence results of epidemiological studies evaluating associations between Pb exposure and cancer, including smoking status, family history of cancer, and co-exposure to other carcinogens. For example, many occupational studies include smelters where exposure to arsenic and other carcinogenic metals (e.g., cadmium) can be correlated with exposure

to Pb. Exposures to Pb occur throughout the lifetime and a cross-sectional evaluation of PbB may not adequately represent the exposure history of the individual.

Measures of Exposure. Numerous studies evaluating cancer in general populations and Pb-exposed workers report PbB as a measure of exposure. A few studies measured exposure by bone Pb concentrations, cumulative blood Pb index, or cumulative exposure (Bhatti et al. 2009; Englyst et al. 2001; Ionescu et al. 2007; Rajaraman et al. 2006); however, these studies did not report PbB.

Characterization of Effects. Numerous epidemiological studies have assessed associations between PbB and cancer. Studies of general populations and workers are briefly summarized in Table 2-46. Studies of general populations include large cross-sectional studies (n=5,482–13,946) of NHANES participants (Cheung et al. 2013; Jemal et al. 2002; Menke et al. 2013; Schober et al. 2006). Mean PbBs in most studies are <10 μg/dL, although in some studies that stratify by PbB, the highest exposure categories are >10 μg/dL (Jemal et al. 2002; Kelly et al. 2013; Schober et al. 2006). Results of two studies with PbB <10 μg/dL show increased risks of all cancer and of lung cancer (Cheung et al. 2013; Schober et al. 2006), although other studies show no increases in cancer risk (Jemal et al. 2002; Khalil et al. 2009; Kelly et al. 2013; Menke et al. 2013; Santibanez et al. 2008; Wiesskoph et al. 2009). Results of occupational exposure studies are mixed and do not establish a pattern of effects of exposure-response relationships. PbBs in these studies generally are >40 μg/dL. Studies have reported associations between PbB and all cancer (Anttila et al. 1995; Lundstrom et al. 1997; Lustberg and Silbergeld 2002; McElvenny et al. 2015; Wong and Harris et al. 2000), cancers of the bronchus, trachea, and lung (Anttila et al. 1995; Chowdhury et al. 2014; Kim et al. 2015; Lundstrom et al. 1997; McElvenny et al. 2015; Steenland and Boffetta 2000), cancer of the larynx (Chowdhury et al. 2014), stomach cancer (Cooper et al. 1985; Steenland and Boffetta 2000; Wong and Harris et al. 2000), intestinal cancer (Kim et al. 2015), and gliomas (Anttila et al. 1996).

Many studies of occupational cohorts with high exposure to Pb and cancer risks do not report PbB data (Bertazzi and Zocchetti 1980; Bhatti et al. 2009; Cocco et al. 1994, 1997, 1998a, 1998b, 1999a, 1999b; Davies 1984a, 1984b; Dingwall-Fordyce and Lane 1963; Fayerweather et al. 1997; Hu et al. 1999; Jones et al. 2007; Kauppinen et al. 1992; Lin et al. 2009; McElroy et al. 2008; Michaels et al. 1991; Pan et al. 2011; Partanen et al. 1991; Pesch et al. 2000; Rajaraman et al. 2006; Risch et al. 1988; Rousseau et al. 2007; Sankila et al. 1990; Sheffet et al. 1982; Siemiatycki 1991; Sweeney et al. 1986; van Wijngaarden and Dosemeci 2006; Wingren and Englander 1990). Although results of these studies are mixed and

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
General population			
Cheung et al. 2013 Cross-sectional study; n=3,482 (NHANES III)	Mean (SE): 4.44 (0.14)	All cancer	**OR: 1.071 (1.036, 1.106)***
		Lung cancer	**OR: 1.090 (1.054, 1.127)***
Jemal et al. 2002 Cross-sectional study; n=3,592 (NHANES II, age 6 months–74 years)	Quartiles: • Q1: ≤9.8 • Q2: 9.9–12.9 • Q3: 13.0–16.9 • Q4: ≥17.0	All cancer	Adjusted RR Q4: 1.50 (0.75, 3.01)
Khalil et al. 2009 Prospective cohort study; n=532 women (age 65–87 years)	Mean: 5.3 <8 (n=453) ≥8 (n=79)	All cancer	Adjusted HR PbB ≥8 (versus <8): 1.64 (0.73, 3.71)
Kelly et al. 2013 Nested case-control study; n=194 cases NHL; 76 cases MM; and 270 controls (mean age 53.08 years)	Mean (range) • Males: 6.18 (1.54, 67.2) • Females: 5.27 (1.1, 40.1) Quartiles • Q1: 1.54–3.93 • Q2: 3.93–5.88 • Q3: 5.88–8.72 • Q4: 8.75–40.1	NHL	OR Q4: 0.93 (0.43, 2.02) p-trend=0.849
		MM	OR Q4: 1.63 (0.45, 5.94) p-trend=0.533
Menke et al. 2006 Cross-sectional study; n=13,946 (NHANES 1988–1994; mean age 44.4 years)	Mean: 2.58 Tertiles: • T1: <1.93 • T2: 1.94–3.62 • T3: ≥3.62	All cancer	Adjusted OR • T2: 0.72 (0.46, 1.12); p-trend=0.130 • T3: 1.10 (0.82, 1.47); p-trend=0.101

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
Santibanez et al. 2008 Case-control study; n=185 esophageal cancer patients; 285 controls (age 30–80 years)	Low: ≤4.9 High: >4.9	Esophageal	Adjusted OR • Low: 0.79 (0.43, 1.46) • High: 1.69 (0.57, 5.03)
Schober et al. 2006 Cross-sectional study; n=9,757 (NHANES III; age ≥40 years)	Tertiles • T1: <5 (mean 2.6) • T2: 5–9 (mean 6.3) • T3: >10 (mean 11.8)	All cancer	Adjusted RR • **T2: 1.44 (1.12, 1.86)*** • **T3: 1.69 (1.14, 2.52)*** • **p-trend<0.01***
Weisskopf et al. 2009 Prospective study; n=868 men (Normative Aging Study; age 21–80 years)	Mean (SD): 5.6 (3.4) Tertiles: • T1: <4 • T2: 4–6 • T3: >6	All cancer	**Adjusted HR T3: 0.48 (0.25–0.91)*; p-trend=0.02**
Workers			
Anttila et al. 1995 Cross-sectional study; n=20,700 workers (age 30–74 years)	Tertiles: • T1: 0–18.6 • T2: 20.7–39.4 • T3: 41.1–161.6	All cancer	**SMR T2: 1.4 (1.1, 1.8)*** SMR T3: 1.2 (0.9, 1.8)
		Lung, trachea	**SMR T2: 2.0 (1.2, 3.2)*** SMR T3: 1.5 (0.8, 2.1)
Anttila et al. 1996 Cross-sectional study; n=20,741 workers (age 18–74 years)	Tertiles: • T1: 2.1–14.5 • T2: 16.6–26.9 • T3: 29.0–89.1	All nervous system cancers	Adjusted OR T3: 2.2 (0.7, 6.6) p-trend=0.17
		Glioma	**Adjusted OR T3: 11 (1.0, 626)*** **p-trend: 0.037**

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
Chowdhury et al. 2014 Survey study/cross-sectional; n=58,368 male workers (mean age 38.9 years)	Quartiles • Q1: 0–<5 • Q2: 5–<25 • Q3: 25–<40 • Q4: ≥40	Lung	**SMR Q4: 1.20 (1.03, 1.39)***
		Brain	SMR Q4: 0.83 (0.41, 1.49)
		Kidney	SMR Q4: 0.72 (0.33, 1.37)
		Stomach	SMR Q4: 0.92 (0.44, 1.69)
		Esophagus	SMR Q4: 0.65 (0.32, 1.16)
		Larynx	**SMR Q4: 2.11 (1.05, 3.77)***
		Bladder	SMR Q4: 0.70 (0.28, 1.45)
Cooper et al. 1985 Cohort study; n=4,519 battery workers; 2,300 smelters	Mean • Battery (n=1,326): 62.7 • Smelters (n=537): 79.7	All cancer	Battery PMR: 1.06 (0.96, 1.16) Smelters PMR: 1.02 (0.87, 1.19)
		Stomach	**Battery PMR: 1.54 (1.11, 2.15)*** Smelters PMR: 1.03 (0.75, 1.42)
		Large intestine	Battery PMR: 0.98 (0.69, 1.40) Smelters PMR: 1.19 (0.62, 2.28)
		Larynx	Battery PMR: 1.19 (0.54, 2.65) Smelters PMR (95% CI): 1.06 (0.27, 4.21)
		Bronchus, trachea, lung	Battery PMR: 1.16 (0.97, 1.39) Smelters PMR: 1.13 (0.84, 1.51)
		Brain and other CNS	Battery PMR: 1.09 (0.55, 2.18) Smelters PMR: 0.97 (0.32, 3.01)

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
Kim et al. 2015 Cross-sectional study; n=81,067 inorganic Pb workers (54,788 males; 26,279 females; age 20–≤50 years)	Mean (SD) • Males: 8.8 (8.5) • Females 5.8 (5.4) Tertiles: • T1: <10 • T2: 10–20 • T3: >20	All cancer	Males: RR T3: 0.95 (0.56, 1.61) Females RR T3: 1.68 (0.40, 7.13)
		Stomach	Males: RR T3: 0.80 (0.23, 2.71) Females RR T2: 1.82 (0.20, 16.36) Females T3: No cases
		Colo-rectal	Males: RR T3: 1.86 (0.35, 9.79) **Females RR T2: 13.42 (1.21, 149.4)*; p<0.05** Females T3: No cases
		Liver	Males: RR T3: 1.72 (0.72, 4.14) Females T2 RR: 0.83 (0.10, 6.56) Females T3: No cases
		Bronchus, lung	Males: RR T3: 0.46 (0.10, 2.01) **Females RR T2: 10.45 (1.74, 62.93)*; p<0.05** **Females RR T3: 12.68 (1.69, 147.86)*; p<0.05**
Lundstrom et al. 1997 Cross-sectional; n=3979 workers	Mean: • In 1950: 62.2 • In 1987: 33.2	All cancer	**SMR: 1.2 (1.0, 1.5)***
		Lung	**SMR: 2.8 (2.0, 3.8)***
Lundstrom et al. 2006 Nested case-referent study; 3,979 smelter workers	Peak: Cases (n=40): 49.7 Referents (n=114): 55.9	Lung	OR: 0.93 (0.60, 1.44)
Lustberg and Silbergeld 2002 Cross-sectional study; n=4,292; age 30–74 years (NHANES II)	Tertiles: • T1 (n=818): <10 • T2 (n=2,735): 10–19 • T3 (n=637): 20–29	All cancer (rate ratio)	RR T2: 1.46 (0.87, 2.48) **RR T3: 1.68 (1.02, 2.78)***

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
McElvenny et al. 2015 Cohort study; n=9,122 workers; mean age 29.2 years	Mean (SD): 44.3 (22.7) Range: 2.3–321.5	All cancer	**SMR: 1.13 (1.07, 1.20)***
		Esophagus	SMR: 1.05 (0.78, 13.8)
		Stomach	SMR: 1.11 (0.86, 1.43)
		Colon	SMR: 0.98 (0.77, 1.26)
		Kidney	SMR: 1.30 (0.91, 1.86)
		Bladder	SMR: 0.95 (0.67, 1.35)
		Bronchus, trachea, lung	**SMR: 1.42 (1.29, 1.57)***
		Brain	SMR: 0.92 (0.61, 1.38)
Selevan et al. 1985 Retrospective cohort study; n=1,987 male workers	Mean: 56.3	All cancer	SMR: 0.95 (0.78, 1.14)
		Digestive organs	SMR: 0.77 (0.52, 1.10)
		Respiratory system	SMR: 1.11 (0.80, 1.51)
		Kidney	SMR: 2.04 (0.75, 4.44)
		Bladder	SMR: 1.44 (0.53, 3.14)
Steenland and Boffetta 2000 Meta-analysis; data from eight studies on Pb workers; n=36,027 workers	Range of study means: 26–80	Lung	**RR: 1.14 (1.04, 1.25)***
		Stomach	**RR: 1.34 (1.14, 1.57)***
		Brain	RR: 1.06 (0.81, 1.40)
Steenland et al. 1992 Cohort study (same cohort as Selevan et al. 1985); n=1,990 male smelter workers	Mean: 56.3	All Cancer	SMR: 0.98 (0.84, 1.12)
		Colon	SMR: 0.48 (0.22, 0.90)
		Lung	SMR: 1.18 (0.92, 1.48)
		Kidney	SMR: 1.93 (0.88, 3.67)

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
Wong and Harris et al. 2000 Cohort study; n=4,519 battery workers; 2,300 smelters (same cohort as Cooper et al. 1985)	Mean: • All workers: 64.0 • Battery workers: 62.7 • Smelters: 79.7	All cancer	**SMR: 1.045 (1.012, 1.080)***
		Stomach	**SMR: 1.474 (1.125, 1.898)***
		Large intestine	SMR: 0.994 (0.789, 1.235)
		Bronchus, trachea, lung	SMR: 1.164 (1.039, 1.299)
		Kidney	SMR: 0.636 (0.339, 1.087)
		CNS	SMR: 0.748 (0.419, 1.234)

[a]Asterick indicates association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.

CI = confidence interval; CNS = central nervous system; HR = hazard ratio; MM = multiple myeloma; NHANES = National Health and Nutrition Examination Survey; NHL = non-Hodgkin's lymphoma; OR = odds ratio; Pb = lead; PMR = proportionate mortality ratio; RR = rate ratio or relative ratio; SD = standard deviation; SE = standard error; SMR = standard mortality ratio

interpretation may be limited due to confounding factors, associations have been reported between occupational exposure to Pb and cancer, including overall cancer mortality and cancers of the lung, brain, stomach, kidney, and bladder.

Mechanisms of Action. Numerous mechanisms for Pb-induced carcinogenicity have been proposed (EPA 2014c); however, it is likely that a combination of mechanisms, rather than a single mechanism, is involved. Although Pb is considered to be only weakly mutagenic, it has been shown to produce DNA damage (single and double strand breaks), sister chromatid exchanges (SCEs), chromosome aberrations, micronuclei (MN) formation, and cytogenetic damage. Epigenetic mechanisms (e.g., changes in gene expression in the absence of changes to DNA), post-translational alterations to protein structure, and immune modulation of tumorigenesis in response to Pb-induced ROS oxidative damage and inflammation have also been proposed as possible mechanisms involved in Pb-induced carcinogenesis.

2.20 GENOTOXICITY

The genotoxicity of Pb has been studied in Pb workers and the general population, in *in vivo* animal models, and *in vitro* cultures of microorganisms and mammalian cells. For the following discussions, data from epidemiological studies on genotoxicity were obtained from the primary literature. Information on *in vitro* studies and *in vivo* animal studies was taken from comprehensive reviews of Pb genotoxicity (EPA 2014c; Garcia-Leston et al. 2010; IARC 2006; NTP 2003).

Epidemiological Studies

Overview. Epidemiological studies have examined genotoxic effects associated with Pb exposure in adults (general populations and workers) and children. Most studies were conducted in small populations of workers. Numerous studies with PbB $\geq$10 μg/dL report positive associations for exposure to Pb and genotoxic endpoints (gene mutation, DNA damage, SCE, MN formation, and DNA methylation); results are generally positive, although some negative associations have been reported. Few epidemiology studies have evaluated genotoxicity at PbB $\leq$10 μg/dL.

The following genotoxic effects have been associated with PbB:

- ≤10 μg/dL:
  - Gene mutation.
  - DNA damage; evaluated in a few studies with mixed results.
  - DNA methylation; positive results, corroborated in a few studies.
- >10 μg/dL:
  - DNA damage; corroborated in numerous studies.
  - Decreased telomere length.
  - Chromosomal aberrations; evaluated in numerous studies with mainly positive results.
  - Sister chromatid exchange; evaluated in numerous studies with mainly positive results.
  - Micronuclei formation; evaluated in numerous studies with mainly positive results.

Measures of Exposure. Studies evaluating the association between genotoxic effects and Pb exposure typically evaluate exposure by measurement of PbB.

Confounding Factors. Most epidemiological studies evaluating genotoxic effects were conducted in worker populations. Therefore, potential co-exposure to other genotoxic compounds (such as arsenic) could occur, confounding interpretation of results. In addition, many studies were conducted in small populations (n<100).

Characterization of Effects. General trends for studies demonstrating associations between PbB and genotoxic effects are shown in Table 2-47. Additional study details are provided in the *Supporting Document for Epidemiological Studies for Lead,* Table 14. Although few studies have evaluated genotoxic effects at PbB ≤10 μg/dL (see discussion below), numerous studies in adult workers with mean PbBs ranging from 20 to >50 μg/dL provide evidence of increased DNA damage, chromosomal aberrations, SCEs, and MN. One study reported decreased telomere length in workers (Pawlas et al. 2016). A few studies in workers reported negative findings for chromosomal aberrations (Anwar and Kamal 1988; Bulsma and DeFrance 1976; Mäki-Paakkanen et al. 1981; Schwanitz et al. 1975) and SCEs (Grandjean et al. 1983; Mäki-Paakkanen et al. 1981); however, positive results for these endpoints were reported in other studies at similar PbBs.

Table 2-47. Overview of Epidemiology Studies Evaluating Genotoxicity Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Gene mutation	Van Larebeke et al. 2004
	DNA damage/repair	Jasso-Pineda et al. 2012
	Decreased telomere length	Pawlas et al. 2015
	DNA methylation	Hanna et al. 2012; Li et al. 2016; Pilsner et al. 2009
	MN	Mielzynska et al. 2006
>10–30	DNA damage/repair	Chinde et al. 2014; Danadevi et al. 2003; Jannuzzi and Alpertunga 2016; Kašuba et al. 2012; Kayaalti et al. 2015b; Méndez-Gómez et al. 2008; Shaik and Jamil 2009
	Chromosomal aberrations	Pinto et al. 2000
	SCE	Anwar and Kamal 1988; Pinto et al. 2000
	MN	Chinde et al. 2014; Khan et al. 2010b; Kašuba et al. 2012;Nordenson et al. 1978; Pinto et al. 2000
>30–50	DNA damage/repair	Fracasso et al. 2002; Grover et al. 2010
	Decreased telomere length	Pawlas et al. 2016
	Chromosomal aberrations	Forni et al. 1976; Grover et al. 2010; Schwanitz et al. 1970
	SCE	Duydu et al. 2001, 2005; Wiwanitkit et al. 2008; Wu et al. 2002
	MN	Grover et al. 2010; Hamurcu et al. 2001; Minozzo et al. 2004
>50	DNA damage/repair	de Restrepo et al. 2000
	Chromosomal aberrations	Al-Hakkak et al. 1986; Forni et al. 1976; Huang et al. 1988; Nordenson et al. 1978; Schwanitz et al. 1970
	SCE	Huang et al. 1988
	MN	Shaik and Jamil 2009; Singh et al. 2013; Vaglenov et al. 1998, 2001

DNA = deoxyribonucleic acid; MN = micronuclei; PbB = blood lead concentration; SCE = sister chromatid exchange

Results of genotoxicity studies conducted in small populations of children (n=12–103) are inconsistent; for study details, see the *Supporting Document for Epidemiological Studies for Lead,* Table 14. Mixed results were observed for studies on DNA damage, with positive associations at mean PbBs of 7.3 and 28.5 µg/dL (Méndez-Gómez et al. 2008; Jasso-Pineda et al. 2012) and no associations at a mean PbB of 19.5 µg/dL (Méndez-Gómez et al. 2008). No associations were observed for chromosome aberrations at a PbB range of 12–33 µg/dL (Bauchinger et al. 1977) and for SCE at mean PbBs of 7.69 and 62.7 µg/dL (Dalpra et al. 1983; Mielzynska et al. 2006). MN formation was positively associated with a mean PbB of 7.69 µg/dL (Mielzynska et al. 2006), and altered DNA methylation was found in newborns at mean umbilical cord PbB of 6.6 µg/dL (Pilsner et al. 2009).

Effect at Blood Pb Levels ≤10 µg/dL. Results of studies evaluating genotoxic effects of PbB ≤10 µg/dL are summarized in Table 2-48, with study details provided in the *Supporting Document for Epidemiological Studies for Lead,* Table 14. Few studies have evaluated genotoxicity at PbB ≤10 µg/dL. Some endpoints were only evaluated in a single study; therefore, it is difficult to draw conclusions. With the exception of a large study conducted in NHANES participants (Zota et al. 2015), genotoxic effects were evaluated in small study populations (n=12–103). Gene mutations were observed in a single study of Finnish women at a PbB range of 1.6–5.2 µg/dL (Van Larebeke et al. 2004). Results of studies on DNA damage are mixed, with no associations in adult workers at PbB means of 2.1–4.4 µg/dL (Al Bakheet et al. 2013; Hengstler et al. 2003), and positive associations in a small study of children with a mean PbB of 7.3 µg/dL (Jasso-Pineda et al. 2012). No effect on telomere length was observed in a large NHANES study of adults with a mean PbB of 1.67 µg/dL (Zota et al. 2015). No associations were observed for SCE in a single study in workers with a mean PbB of 9.3 µg/dL and for MN in children with a mean PbB of 7.69 µg/dL (Meilzynska et al. 2006; Wu et al. 2002). Studies on DNA methylation showed positive associations in adult women undergoing *in vitro* fertilization (median PbB 2.88 µg/dL), in children (mean PbB 1.36 µg/dL), and in newborns (mean umbilical cord PbB 6.6 µg/dL) (Hanna et al. 2012; Li et al. 2016; Pilsner et al. 2009).

***In Vivo* Animal Models and I*n Vitro* Cultures of Mammalian Cells and Microorganisms.** Numerous studies have investigated the genotoxicity of Pb using *in vivo* animal models and cultured mammalian cells and microorganisms. Rather than reviewing these numerous studies, an overview of findings is summarized below. This information was taken from the following reviews: EPA 2006, 2014c; IARC 2006; NTP 2016.

In vivo studies in animals. DNA damage has been observed in several *in vivo* exposure studies in rodents. DNA damage (single strand breaks), as measured in comet assays, was observed in various organ systems, bone marrow, leukocytes, and spermatozoa of mice and rats following repeated inhalation or oral exposures to Pb or Pb acetate. Global hypomethylation in hepatic DNA of rats was observed following single intravenous injection of Pb nitrate; hypomethylation was associated with an increase in cell proliferation. Exposure to Pb compounds is correlated with increased DNA synthesis and cell proliferation in the mammalian liver following intravenous injection. Numerous studies have assessed Pb compounds for chromosomal damage. Chromosomal aberrations were observed in bone marrow cells and spermatocytes of mice and rats following single or repeated exposure (intraperitoneal, gavage, dietary); however, the increase in aberrations did not consistently demonstrate dose-dependence.

Table 2-48. Results of Genotoxicity Studies at Blood Lead Concentration (PbB) ≤10 µg/dL

PbB or range (µg/dL)	Population (n)	Gene mutation	DNA damage	Telomere length	SCE	MN	DNA methylation	Reference
1.6–5.2	Women (99)	↑	NA	NA	NA	NA	NA	Van Larebeke et al. 2004
2.1	Men (40)	NA	0	NA	NA	NA	NA	Al Bakheet et al. 2013
3.28	Children (99)	NA	NA	↓	NA	NA	NA	Pawlas et al. 2015
4.4	Workers (78)	NA	0	NA	NA	NA	NA	Hengstler et al. 2003
7.3	Children (12)	NA		NA	NA	NA	NA	Jasso-Pineda et al. 2012
1.67	Adults (6,796)[a]	NA	NA	0	NA	NA	NA	Zota et al. 2015
9.3	Workers (34)	NA	NA	NA	0	NA	NA	Wu et al. 2002
7.69	Children	NA	NA	NA	NA	0	NA	Meilzynsja et al. 2006
>0.73	Women (43)	NA	NA	NA	NA	NA	↓	Hanna et al. 2012
1.45	Adults (78)[b]	NA	NA	NA	NA	NA	↓	Li et al. 2016
6.6[c]	Newborns (103)	NA	NA	NA	NA	NA	↑↓	Pilsner et al. 2009

[a]NHANES participants.
[b]Prospective study; genotoxicity assessed in adults and evaluated against PbB obtained during childhood (birth–78 months).
[c]Umbilical cord PbB.

↑ = increase observed for specific effect; ↓ = decrease observed for specific effect; ↑↓ = decreased DNA methylations at some differentially methylated regions, and increased DNA methylation at other regions; 0 = no effect observed; DNA = deoxyribonucleic acid; MN = micronuclei; NA = not assessed; NHANES = National Health and Nutrition Examination Survey; SCE = sister chromatid exchange

Exposure to Pb compounds has been associated with SCEs in bone marrow of mice and rats following intravenous exposure. Studies assessing Pb compounds for MN formation in bone marrow erythrocytes of rats and mice were positive for multiple exposure routes (gavage, drinking water, intraperitoneal).

In vitro studies in human cell lines. *In vitro* studies in human cells lines have yielded mixed results. Pb acetate was weakly mutagenic in keratinocytes in the presence of 6-thioguanine, but not mutagenic in human foreskin, fibroblasts, or lung carcinoma cells. Results of assays assessing Pb compounds for DNA damage in human cell cultures were inconsistent. Double or single DNA strand breaks have been observed in peripheral blood lymphocytes, endothelial cells, hTERT-immortalized human skin fibroblasts, and HepG2 cells, but not in HeLa cells. DNA-protein crosslinks were observed in lymphoma cells exposed to 100 μM Pb acetate, although cross-links were not observed for Pb nitrate at concentrations up to 10,000 μM. Studies investigating SCEs and MN formation in human lymphocytes were positive following exposure to Pb nitrate and Pb chloride; however, no SCEs were observed in human lung cells or primary lymphocytes exposed to Pb. Interpretation of *in vitro* studies is challenging because concentrations used in these studies typically are very high and are not relevant to environmental or occupational exposures. As discussed in Section 3.1.2 (Toxicokinetics, Distribution), >99% of Pb in blood is bound to erythrocytes, leaving <1% available in plasma. Thus, plasma levels of Pb are far lower (at least two orders of magnitude) than the concentrations examined in *in vitro* studies in human cell lines. This leads to the introduction of considerable bias when interpreting study results (Bannon and Williams 2017).

In vitro studies in prokaryotic and mammalian cells. Mutagenicity tests of Pb compounds in prokaryotic organisms have mostly yielded negative results. Studies assessed gene mutation and DNA damage in *Salmonella typhimurium*, *Escherichia coli,* and *Bacillus subtilis* and gene conversion and mitotic recombination in *Saccharomyces cerevisiae* in the presence or absence of metabolic activation. The only Pb compound that yielded positive results for gene mutation in *S. typhimurium* and *E. coli* was Pb bromide. Results of *in vitro* studies in mammalian cells for Pb compounds are mixed. Mutagenicity assays (hypoxanthine phosphorybosyl transferase [HPRT] and glutamate pyruvate transaminase [gpt] assays) were mutagenic in Chinese hamster ovary (CHO) and CHV79 cells at higher concentrations (>100 μM) and negative at lower concentrations (<100 μM). Pb chloride was the only Pb compound that was consistently mutagenic (gpt assay) in CHO cells at low concentrations (0.1–1.1 μM; equivalent to 2.3–23 μg/dL). Comet assays assessing Pb acetate for DNA damage (single strand breaks) in undifferentiated PC12 cells and mouse bone marrow mesenchymal stem cells were positive. Concentration-dependent increases in DNA-protein crosslinks were observed in hepatoma cells exposed

to Pb nitrate, although Pb acetate did not induce single or double DNA strand breaks or DNA crosslinks in CHV79 cells. Exposure to Pb nitrate or Pb glutamate did not induce chromosomal aberrations in CHO cells. Assays assessing Pb compounds for SCEs in CHV79 cells were negative when fewer cells per concentrations were utilized (25–30 cells), but were positive when the number of cells per concentration was increased (100 cells). Conflicting results were reported for MN formation in Chinese hamster cells.

Mechanisms of Action. Several mechanisms of action are likely involved in the genotoxic effects of Pb (EPA 2014c; IARC 2006; NTP 2016). Studies in occupationally exposed populations have found significant correlations between DNA breaks, decreased glutathione levels in the lymphocytes, and increased production of ROS, which may indicate oxidative stress as a possible mechanism for this response. The production of ROS after Pb exposure is a multi-pathway process, which results from oxidation of ALA, membrane and lipid oxidation, NAD(P)H oxidase activation, and antioxidant enzyme depletion. Disruption of functional metal ions that form enzymes (superoxide dismutase [SOD], catalase [CAT], and glutathione peroxidase [GPx]) may occur as part of this process.

2.21 GENERAL CELLULAR MECHANISMS OF ACTION

2.21.1 Perturbation of Ion Homeostasis

Pb exerts many of its adverse effects by perturbing ion homeostasis. This perturbation occurs when Pb displaces other metal ions such as iron, calcium, zinc, magnesium, selenium, and manganese, interfering with the critical biological processes mediated by the ions themselves or by enzymes and proteins that require these ions (reviewed by EPA 2014c; Flora et al. 2012). Among the biological processes that Pb has been shown to affect via its impact on ion homeostasis are: calcium homeostasis; transportation of ions across cell membranes; cellular energetics; and the functioning of numerous proteins involved in cell signaling, growth and differentiation, gene expression, energy metabolism, and biosynthetic pathways.

Calcium Homeostasis. Many of Pb's adverse effects can be traced back to its ability to displace calcium, leading to perturbations of numerous calcium-dependent cellular functions, including energy metabolism, apoptosis, cellular motility, signal transduction, and hormonal regulation (reviewed by EPA 2014c). In addition, intracellular migration of Pb has been shown in several cell lines (HEK293, HeLa, and PC12) to occur via calcium channels; higher Pb permeation correlated with lower calcium concentrations, suggesting that Pb competed with calcium for the channel binding sites.